ECONOMIC EVALUATION AND ASSESSMENT OF EARLY TOXICITY OF HYPOFRACTIONATED RADIOTHERAPY COMPARED TO STANDARD FRACTIONATION IN BREAST CANCER

DEPARTMENT OF RADIOTHERAPY
CHRISTIAN MEDICAL COLLEGE
VELLORE 632004

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD BRANCH IX RADIOTHERAPY
EXAMINATION APRIL 2015

TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032.

CHRISTIAN MEDICAL COLLEGE, VELLORE

DEPARTMENT OF RADIOTHERAPY

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Guide

Dr.Selvamani B

Professor

Department of Radiotherapy

Christian Medical College

Vellore, India – 632004

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Principal

Christian Medical College

Vellore,India- 632 004

Head of the Department

Dr.Selvamani B

Prof and Head of the department

Department of Radiotherapy

Christian Medical College

Vellore, India - 632004

Certificate

I K.Chandralekha, PG Registrar ,Department of Radiation therapy ,Christian Medical College Vellore hereby declare that the dissertation titled **"Economic Evaluation And Assessment Of Early Toxicity Of Hypofractionated Radiotherapy Compared To Standard Fractionation In Breast Cancer "** is a bonafide work done by me for partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2015.

DR.K.CHANDRALEKHA

PG REGISTRAR ,

DEPARTMENT OF RADIOTHERAPY,

CHRISTIAN MEDICAL COLLEGE,

VELLORE

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Additional Vice Principal (Research)

April 25, 2014

Dr. K. Chandralekha
PG Registrar
Department of Radiotherapy
Christian Medical College,
Vellore 632 004

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Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
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We approve the project to be conducted as presented.

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A sum of 23,000/- INR (Rupees Twenty Three Thousand only) will be granted for 6 months.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
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Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

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CONTENTS

ABSTRACT

Economic Evaluation And Assessment Of Early Toxicity Of Hypofractionated Radiotherapy Compared To Standard Fractionation In Breast Cancer

Chandralekha*, Selvamani.B, Balukrishna, Jasmine Prasad, Department of Radiotherapy,

Christian Medical College, Vellore

Introduction: Breast cancer is the most frequent cancer among women with the global incidence in women to be 25.2% of all reported new cancers. In India, breast cancer is the most common cancer at 27% of all new cancers . Breast cancer is associated with substantial medical and economic burden and henceforth the management of breast cancer accounts for a large percentage of health care budget. Radiation therapy as an integral part in the multi-modality management of breast cancer significantly reduces the locoregional recurrence and also improves the overall survival. To overcome the economic burden related to radiotherapy in breast cancer various hypofractionated schedules like 39 Gy in 13 fractions, 40 Gy in 15 fractions were tried and have proven to achieve similar local control rates, survival rates and cosmetic outcome. This study aims to do the economic evaluation and to assess the acute toxicities associated with 40 Gy in 15 fraction(hypofractionated regimen).

Aims and objectives: To analyse the cost difference in breast cancer radiotherapy between conventional fractionation and hypofractionated radiotherapy.

The study also aims at assessing the early toxicities of patients receiving post mastectomy radiotherapy.

Methods and materials: This Prospective study group consisted of 30 consecutive patients seen in the Radiation therapy department of Christian Medical College, Vellore from February to August 2014, treated with standard fractionation and hypofractionated post mastectomy radiotherapy by conventional technique. Each patient was interviewed using a pilot tested questionnaire to collect data on the health economics. The costs imparted to the patient were classified as direct and indirect costs. The cost effect for each was assessed at the end of the treatment. The occurrence of early toxicity in patients treated with standard and hypofractionated radiotherapy was recorded and analysed using RTOG acute skin toxicity criteria.

Results: Twenty three patients were included in the 40 Gy in 15 fractions arm and 7 patients were in the 50 Gy in 25 fractions arm. Of the 30 patients 15 were treated in the Cobalt and 15 were treated in Linear accelerator. The analysis showed that there was significant reduction in costs in hypofractionation with conventional treatment in Cobalt 60. The difference in Linear accelerator was not found to be significant.

Conclusion : Adoption of hypofractionated radiotherapy in breast cancer treatment can lead to significant reduction in resource utilisation and is especially pronounced for conventional radiotherapy settings with high patient loads.

Keywords : Carcinoma Breast PostMastectomy Radiotherapy Hypofractionation

1 . AIMS & OBJECTIVES

AIM:

To analyse the financial benefits of the cost difference in breast cancer radiotherapy between conventional fractionation and hypofractionated radiotherapy. The study also aims at assessing the early toxicities of patients receiving post mastectomy radiotherapy.

Primary objective:

Report the difference in mean cost per patient for treatment with standard and Hypofractionated post mastectomy radiotherapy for carcinoma breast (COST MINIMISATION).

Secondary objective:

To assess early toxicity in patients treated with standard and hypofractionated radiotherapy.

2. INTRODUCTION:

Breast cancer is the most frequent cancer among women according to the Globocan 2012 update. The incidence of breast cancer in women worldwide is reported to be 25.2% of all new cancers and is expected to increase much more by 2020. (1) In India, breast cancer is the most common cancer contributing to 27% of all new cancers in women (1).

Taking into account cancers worldwide, the total economic burden of this disease was estimated to be in the range US dollar 300-400 billion in 2001 [about US dollar 100-140 billion as direct costs and the rest as indirect costs (2). There is significant medical and economic burden associated with breast cancer and it accounts to large expenses on the public, but the expenses have been difficult to gauge.

Radiation therapy is an integral part of the multi-modality management of breast cancer. The increase in the incidence of the breast cancer has contributed significantly to the rising numbers of patients receiving post mastectomy radiotherapy. The conventional dose of radiotherapy in breast cancer is to deliver 50 Gy in 25 fractions over 5 weeks.

In view of the prolonged duration of treatment and machine availability, various hypofractionated schedules have been investigated and it is proven to be advantageous by many randomised trials. (3) This lesser treatment schedule is not only favourable for the patients by decreasing the number of hospital visits, but also beneficial for the health services with limited resources, waiting list in the hospital etc., by reducing the machine time and human resources. This time saved may be adequately utilised for the treatment of another patient. Moreover, the total treatment time, that is, the daily treatment time multiplied by the number of fractions attributes to the cost of radiotherapy.

Hence, a reduction in the daily treatment time and /or a decrease in the number of fractions would in turn reduce the cost of radiotherapy.

These short course treatments make an impact by achieving similar local control rates, survival rates and cosmetic outcome with the great advantage in reducing the number of visits to the hospital to the patients and to the health services by improving machine utilisation.

The aim of this study is to do the economic evaluation of hypofractionated radiotherapy along with assessment of the acute toxicities associated with it.

Review of Literature

3. LITERATURE REVIEW

3.1 BREAST CANCER STATISTICS:

The most frequent cancer among women is breast cancer with the Globocan 2012 update showing the global incidence of breast cancer in women to be 25.2% of all reported new cancers (Fig.3.1.1) (1). Also in India, breast cancer has become the most common cancer at 27% of all new cancers in women (1).

Breast cancer is also the most common cause of cancer related mortality in women (14.7%) worldwide (Fig.3.1.2).

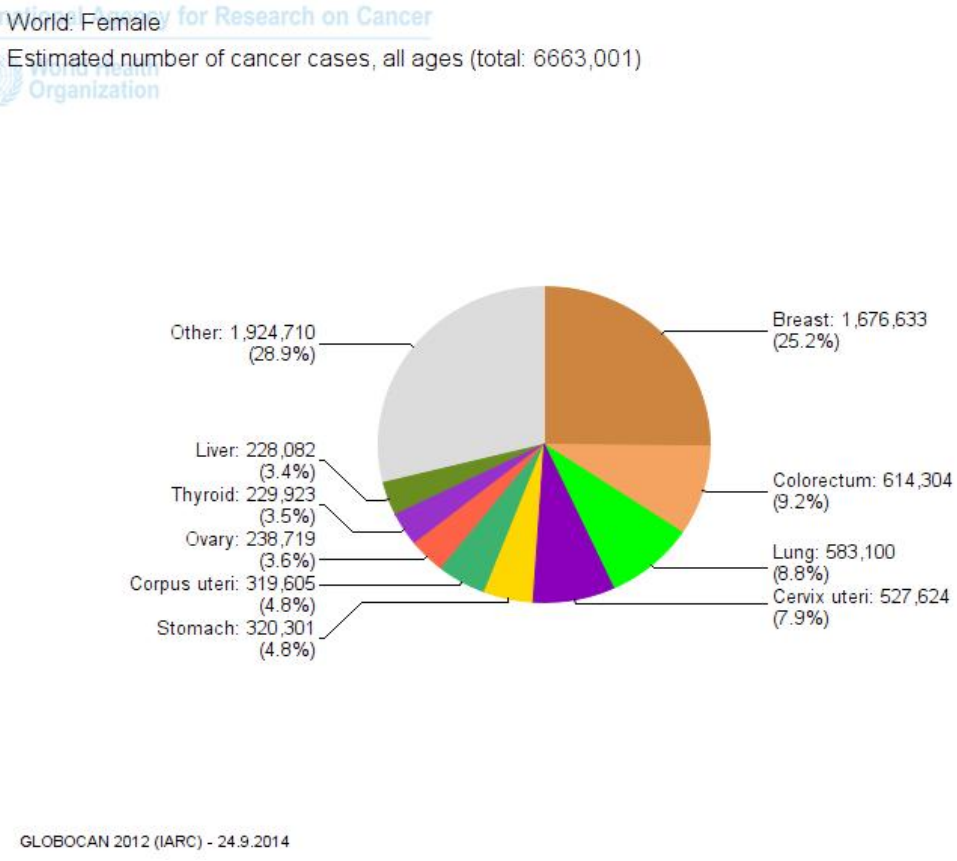


Fig 3.1.1: Cancer Incidence in Women, World - GLOBOCAN 2012

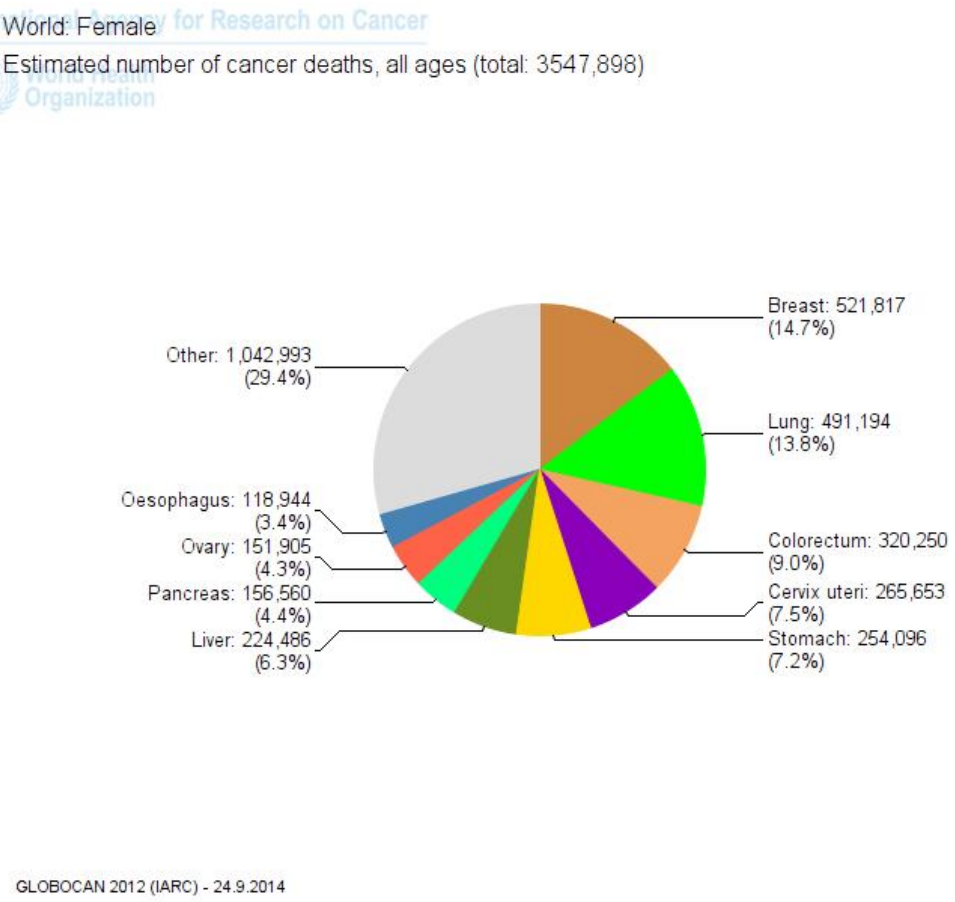


Fig 3.1.2: Cancer Mortality in Women,World - GLOBOCAN 2012

Incidence rates of breast cancer vary from 19.3 per 100,000 women in Eastern Africa to 89.9 per 100,000 women in Western Europe, and are almost high (>80 per 100,000) in developed countries (except Japan) and low (<40 per 100,000) in most of the developing countries of the world (2) (Fig.3.1.3). In developed regions mortality rates is much less (approximately 6–19 per 100,000) because of the more favourable survival of breast cancer.

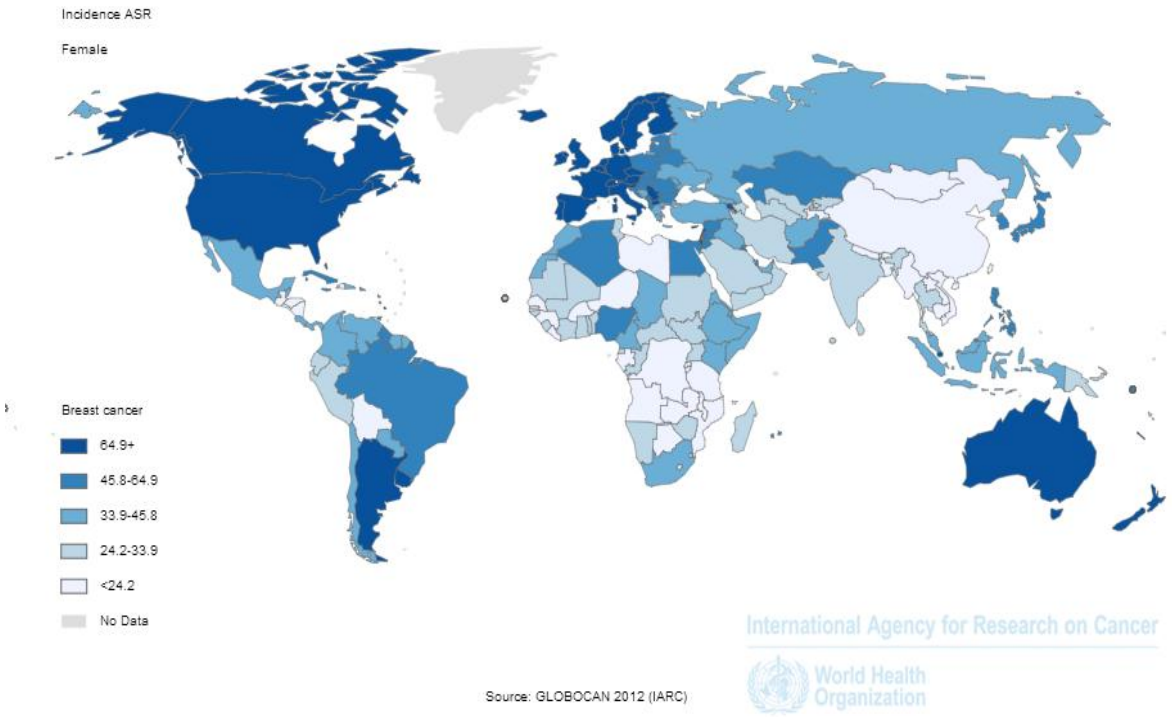


Fig 3.1.3: Age standardised incidence of breast cancer across the world

By 2020, 70% of the world's cancer cases will be in poor countries, with a fifth in India (2). In 2011, ICMR conducted an analysis of cancer cases among women in Delhi, Chennai, Bangalore and Mumbai from 1982 to 2005. The study showed that 10 per 100,000 women got breast cancer until about 10 years ago compared with 23 per 100,000 later on (2). It was predicted in this report that by 2020, breast cancer will overtake cervical cancer as the most common type of cancer among all women in India.

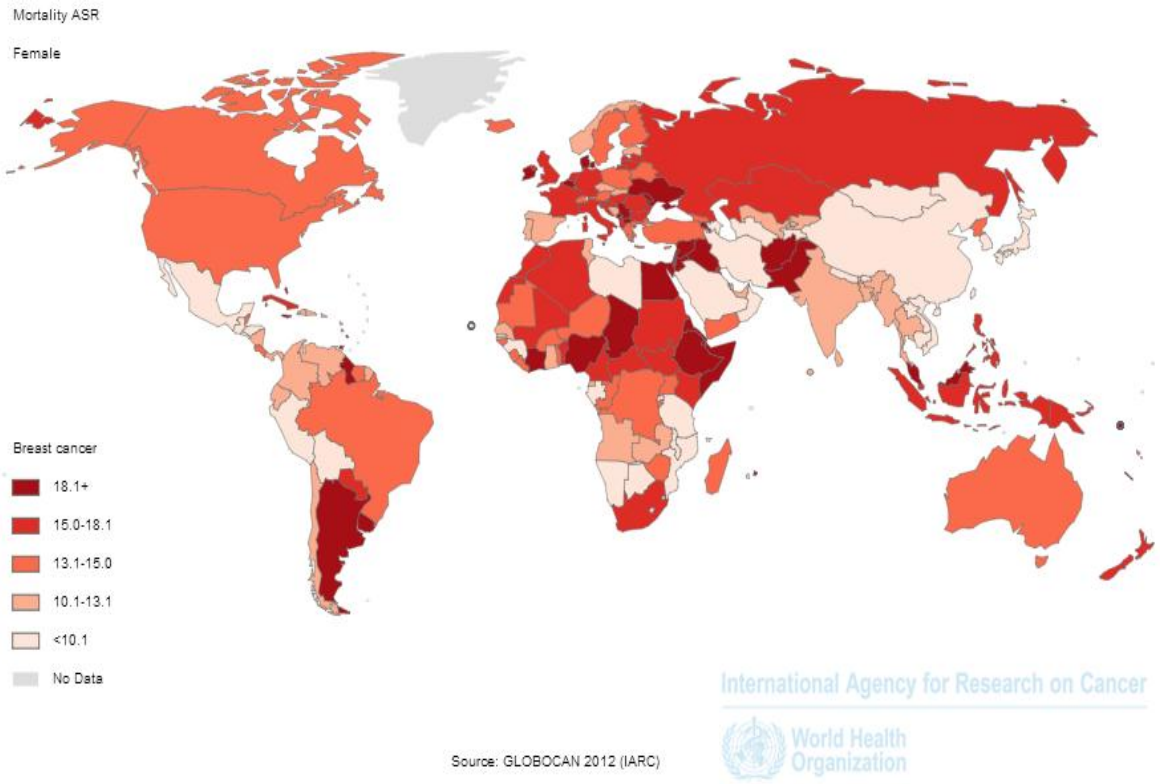


Fig 3.1.4: Age standardised mortality rates of breast cancer across the world

There is an increasing trend in breast cancer incidence which may be due to increased awareness and advanced diagnostic modalities, but the corresponding decreasing trend in cervical cancer suggests that it is a true increase. This increase in incidence of breast cancers may be due to genetic and environmental factors. Etiologically though women in poor countries are less prone for breast cancers than those in the west, they are more likely to die of it because of late presentation. While incidence is about 130 per 100,000 women in the USA, it is only about 19 per 100,000 in India (4). But the chances of surviving cancer in a low-income or middle-income country are much worse than in the UK or USA. Fig 3.1.4 shows the age standardised mortality rates of breast cancer across the world.

3.2 FINANCIAL SCENARIO IN INDIA:

The most probable reason for the scenario above said is that women seek medical care very late. Poor awareness of breast cancer among public, inhibition, reluctance, financial constraints of the people, staying away from home, inability to access care and following alternative medicine are the most common reasons for presenting late to medical care. Financial constraints also prevent patients from having the best treatment, for e.g. Trastuzumab(5). Women delay seeking medical care and hence often present with large lumps . Even when patients finally do seek care, they often cannot complete the treatment due to financial constraints.

Most of the patients are farmers or labourers or daily wage makers, who land in major Government and Trust hospitals. Though the concessions and insurances are offered by major Government and Trust hospitals, transport and accommodation costs can hamper patients' finances.

Even with patients who get comprehensive insurance policies, people are found to suffer financial hardships. Though insurance is provided to decrease the financial burden, lot of out of pocket costs are met by the patient and family in addition to the loss of income by them and the low socio economic status people are the most affected ones. Also, the patients have to spend quite a large sum for accommodation, food, medicines including the expenses for the accompanying person which are not covered by insurance.

3.3 MANAGEMENT OF BREAST CANCER: AN OVERVIEW

Management of invasive breast cancer comprises a multimodality approach with surgery, chemotherapy, radiation therapy hormonal therapy and targeted therapy all playing integral parts.

The factors that influence the choice of treatment include age, pathological stage of the cancer especially tumour size and nodal status, biological prognostic factors and hormonal receptor status. Various combinations and the sequences of the multimodality treatment in addition to surgery are determined by these factors. Introduction of multimodality treatment reduced breast cancer mortality by 18% and improved overall survival (5).

The primary modality of management with surgery for invasive breast carcinoma has undergone a shift over the years from radical mastectomy to breast conservation surgery and sentinel lymph node biopsy. Similarly locally advanced breast cancers are made feasible for breast conservation surgery after neoadjuvant chemotherapy following good response to chemotherapy. The adjuvant therapy of breast cancer has also improved with the advent of new chemotherapeutic, hormonal and targeted agents.

Radiation therapy has also advancements and amendments in the technique of delivery from conventional through 3D conformal techniques to IMRT and recently accelerated partial breast irradiation. Besides the techniques there has also been a transition in the dose and fractionation of the radiotherapy delivered.

3.4 ROLE OF RADIATION THERAPY IN BREAST CANCER

Radiation therapy has been a modality in the treatment of the breast cancer ever since the discovery of X-rays and its tumoricidal properties were discovered. It is an integral part in the management of both early as well locally advanced breast cancers. It has been established that post operative radiotherapy significantly reduces the locoregional recurrence and also improves the local control which indirectly increases the cancer specific and overall survival. The importance of local control in breast cancer survival cannot be discounted.

In early breast cancers it is used as adjuvant therapy to deliver whole breast radiation followed by boost to the lumpectomy site. In locally advanced cancers it is use to deliver radiation to the chest wall after mastectomy. The inclusion of regional lymphatic region is based on the number of axillary lymph nodes positive for tumour deposits after axillary clearance or on the basis of use of neoadjuvant chemotherapy.

A total of 9422 patients from 15 randomised trials were included in the analysis by Vin Hung et al and it was concluded that the relative risk of ipsilateral breast recurrence for omitting radiotherapy was 3 and relative risk of mortality on omitting radiotherapy was 1.086 with a relative excess of 8.6% in mortality on omitting radiotherapy in breast conservation therapy (6).

The indications for post mastectomy radiation therapy have been defined from the results of various randomized trials like the Danish trial and British Columbia trial(7,11). Benefit in terms of local control and survival was found in stages II / III and node positive breast cancers. Studies showed that the addition of post mastectomy radiotherapy reduced loco

regional recurrence rate by 2/3rd to3/4th when compared to the groups that did not receive radiotherapy (7,8). Decrease in local recurrences and improvement in overall survival with radiation therapy have been established in many randomized trial involving both premenopausal and postmenopausal breast cancer women (7-11).

Findings from 78 randomized clinical trials were analysed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (12), these trials were done for evaluating the extent of surgery and the use of radiation therapy. The analysis revealed improved local control at 5 years and significant improvement in survival and overall survival at 15 years. Moreover the Trialsists' were established that the absolute reduction in the 5-year rate of local recurrence was proportional to the absolute reduction in 15-year breast-cancer mortality. Modality of therapies with minimal or no effect on reducing the 5-year rate of local recurrence had no benefit in decreasing 15-year cancer related mortality; however, treatments that resulted in improvement in the 5-year rate of local recurrence also resulted in a reduction in breast-cancer mortality at 15 years (Fig 3.4.1).

Regardless of the method of achieving the reduction (i.e., by extensive surgery or by the addition of radiotherapy) the absolute benefit for cancer related mortality was similar for a given reduction in local recurrence. Among treatments that had more than a 10% reduction in the 5-year risk of local recurrence, breast-cancer mortality was reduced by 1.6% at 5 years, 3.7% at 10 years, and 4.9% at 15 years.

The trials in the EBCTCG meta-analysis that studied had demonstrated significant improvement in 15-year absolute overall survival by the addition of radiotherapy after breast-

conservation surgery, by 5.3% (P = 0.005), and after mastectomy in node-positive patients, by 4.4% (p = 0.001) (10).

On the other hand, the role of post mastectomy radiotherapy in T1/T2 tumour, grade grade 2 with 1-3 lymph nodes positive is still debatable. The indication in this group of breast cancers is expected from the results of the on-going Supremo trial(13). Various factors such as size of tumour (>4 cm), close/positive margins, lymph vascular invasion, extra capsular extension, ER/PR/Her2 neu status, grade of tumour are known to affect the loco regional recurrence rate, and these factors contribute significantly towards the decision making.

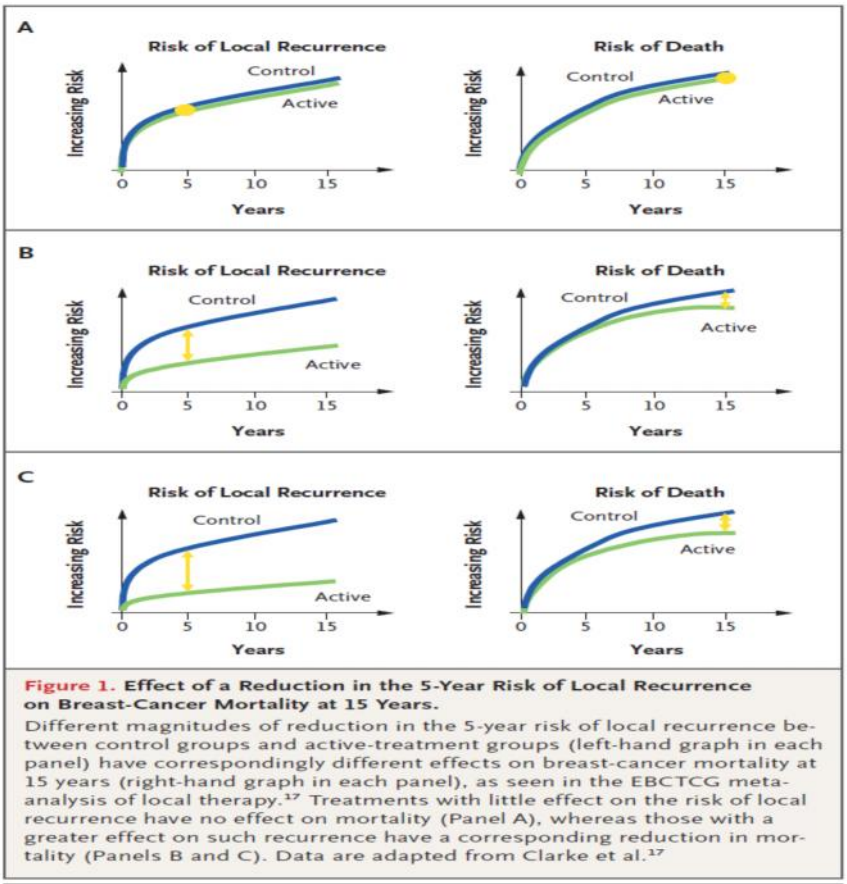


Figure 1. Effect of a Reduction in the 5-Year Risk of Local Recurrence on Breast-Cancer Mortality at 15 Years.
Different magnitudes of reduction in the 5-year risk of local recurrence between control groups and active-treatment groups (left-hand graph in each panel) have correspondingly different effects on breast-cancer mortality at 15 years (right-hand graph in each panel), as seen in the EBCTCG meta-analysis of local therapy.[17] Treatments with little effect on the risk of local recurrence have no effect on mortality (Panel A), whereas those with a greater effect on such recurrence have a corresponding reduction in mortality (Panels B and C). Data are adapted from Clarke et al.[17]

Fig 3.4.1: EBCTCG Meta-Analysis

3.5 RADIOTHERAPY PLANNING AND SIMULATION (19)

Radiotherapy can be delivered in breast cancer by various techniques starting from conventional to IMRT. The preferred position for the treatment of breast cancer patients is in supine position with 90 degrees abduction of the arms on a breast board used as immobilisation. Various commercially available instruments are available to eliminate the slope of the chest wall and to better immobilise the patient.

The entire breast in the case of breast conservation surgery and the chest wall in case of mastectomy patients are included in the radiation portal. The upper margin is kept at the lower edge of the head of the clavicular bone and the lower border is usually kept at a level to include the entire breast which usually comes to about at two to three cm below the inframammary fold. The opposite breast is used as a reference for the lower border in the case of post mastectomy radiation therapy. The midline of the body makes up the medial border and the mid axillary line makes up the lateral border. The field may be extended to include the scar and the drain sties.

The regional lymphatics are included as per the clinical indications. The supraclavicular fossa is included in patients who received neo adjuvant chemotherapy, as the prognostic information usually obtained by axillary dissection is altered in such setting. Supraclavicular fossa is also included in cases where ≥ 4 lymph nodes are positive for metastatic deposits in the axillary dissection.

Indications for axillary radiation therapy include nodal positivity with extracapsular extension, inadequate axillary dissection and patients with estimated probability of nodal involvement greater than 10 to 15% with no axillary dissection.

6 MV x-rays are usually used for the treatment however in cases where the field separation is large, it may result in dose inhomogeneity in which case higher energy X rays may be used to achieve a better cosmetic outcome as homogeneity has been correlated with cosmesis. Various techniques like the use of standard wedges, dynamic wedges, MLCs can be used to achieve dose homogeneity in the breast. Use of bolus is not necessary in cases of T1-2 tumors whereas it may be necessary in the case of locally advanced cancer with the intent of achieving additional radiation dose (boost) at the skin at the site of the surgical scar in mastectomy patients.

It is aimed to keep the amount of lung included in the tangential field at any section to less than 2-3 cm of length from the chest wall lung junction. The amount of lung involved has been correlated with the incidence of radiation pneumonitis. Half beam block is used in the treatment to reduce the incidence of pneumonitis. In cases where the supraclavicular fossa (SCF) is included special attention has to be paid to the field junctions and appropriate techniques employed to avoid excess dose at the junction of the supraclavicular field and the tangential field. The SCF is usually irradiated by an anterior field matched to the tangential field and the dose is delivered at the d max. There are number of ways for matching the tangential fields with the supraclavicular field. By angling the foot of the couch away from the source, the divergence of the tangential fields can be eliminated. The collimator can be rotated to eliminate the overlap at this junction. The inferior divergence of the supraclavicular field can be blocked by placing half beam block for the field.

Motion management techniques are used in breast radiotherapy to counter the effects of breathing on the radiation portals. The technologies available for the same include 4DCT and gating. Breath hold technique is also used as a simpler solution to motion management.

3.6 TREATMENT VOLUMES

In the Danish and EBCTG randomized trials of Post mastectomy radiation therapy (PMRT), RT delivered to the chest wall and surgical scar, including the supraclavicular, infraclavicular, axillary and inframammary lymph nodes demonstrated that radiotherapy results in improvement of local control as well as improvement in overall survival. On the basis of these results, it is well acknowledged that the treatment volume for breast cancer should include the entire chest wall and the scar of the mastectomy surgery. However, with regards to the inclusion of the regional nodal regions in the treatment volume there is still quite a bit of controversy existing.

Positive lymph nodes in the axilla entail the inclusion of ipsilateral supraclavicular fossa in the volume of treatment. But there is wide variation as to whether the Internal Mammary (IM) lymph nodes should be included. This controversy is partly in view of the potential toxicity particularly in the case of left sided breast cancers when the IMN is included in the radiation portals. In addition the added benefit of IMN irradiation is very uncertain (15).

In 1996, the European Organization for Research and Treatment of Cancer (EORTC) conducted a trial to evaluate the (protocol 22922/10925) the benefit of including the Internal Mammary nodes and medial supraclavicular nodes in the radiation field for those patients who have axillary node positivity. The medial tumors treated by either breast conservation surgery or by mastectomy were included in this trial.

Another French study also randomized 1334 women of breast cancer who had undergone mastectomy with axillary nodes positivity or central tumors to chest wall and supraclavicular filed irradiation with or without the inclusion of the internal mammary nodal chain in the radiation filed. Preliminary data analysis of this study has not detected any difference in the overall survival (OS) in the two arms (16).

The results of the recently presented MA-20 National Cancer Institute of Canada clinical trial shows an improvement in the DFS in node postive and high risk node negative patients who have been treated by Breast conservation surgery, when the regional nodal regions, including IM lymph nodes, are included while delivering whole breast radiation therapy (17).

Another retrospective study from the MGH has shown similar rates of Loco Regional Relapse (LRR), Disease Free Survival (DFS), and OS in patients with one to three positive lymph nodes treated with chest wall radiation therapy only as compared to those treated with chest wall and nodal irradiation, suggesting that PMRT to the chest wall only may be appropriate for women with tumors <5 cm and one to three positive LNs (18).

Internal mammary chain radiation may be considered in axillary node positivity with central and medial quadrant tumours.

3.7 FRACTIONATION IN BREAST CANCER RADIOTHERAPY:

The conventional radiotherapy regimen after mastectomy for cancer breast delivers 50Gy in 25 fractions of 2 Gy over 5 weeks. In UK and Canada, several trials on alternate schedules (hypofractionation) were done years ago on an empirical basis in breast conservation therapy and based on the results of these trials 40 Gy in 15 fractions over 3

weeks is practiced as standard in these countries. The results of the trials which employed hypofractionated radiotherapy in the treatment of breast cancer are showing favourable outcomes in terms of control of the tumor and also with respect to late adverse effects if the modest increases in size of radiation fractions are adjusted accordingly with appropriate decrease in the total dose of radiation delivered.

Although the hypofractionated radiotherapy schedules have been in wide use in the United Kingdom, the schedule of 40Gy delivered in 15 fractions over 3 weeks has never been tested formally in a randomised trial with the standard fractionation schedules. This lack of strong trial based evidence for hypofractionated radiation raised concerns regarding the safety and the effectiveness of such a schedule when compared with the standard schedule of 50 Gy in 25 fractions. In an effort to address this uncertainty START Trials were initiated by the then UK Coordinating Committee for Cancer Research to test the effects of hypofractionated radiotherapy schedules.

3.8 TRIALS FOR HYPOFRACTIONATED RADIOTHERAPY:

Royal Marsden Hospital/Sutton and Gloucestershire Oncology Centre:(20,21)

In a randomized phase III trial conducted from 1986 - 1998, 1410 patients with early breast cancer were randomized to three arms of different fractionation to assess the effect of fraction size on late change in breast appearance with tumor control as one of the secondary endpoints. The study included only patients with stage 1-3 tumors with only one node positive for metastasis and had undergone only lumpectomy of the tumor site.

The conventional regimen of 50 Gy in 25 fractions over 5 weeks was compared with 39 Gy in 13 fractions, or 42.9 Gy in 13 fractions, both given over 5 weeks. The fraction size of 3 Gy was calculated on the basis of an alpha-beta ratio of 1.8 Gy while the 3.3 Gy fraction

size was arrived at assuming an alpha-beta ratio of 6.0 Gy. The trial was analysed on an intention to treat principle. As per clinical indications, the regional lymphatics were included in the treatment field. Radiation boost was also delivered as indicated in 7 daily fractions to a total dose of 14 Gy.

The primary end point of photographic assessments of the patients were analysed at a median follow up of 8.1 years. Statistically significant difference was seen between the 50 Gy and 39 Gy arm (p=0.01) however the difference between the 50 Gy and 42.9 Gy arm was borderline (p=0.05). The risk of ipsilateral tumour relapse after 10 years was 12.1% in the 50 Gy arm , 14.8% in the 39 Gy arm and 9.6% in the 42.9 Gy arm at a median follow-up of 9.7 years (difference between 39 Gy and 42.9 Gy groups, chi^2 test, p=0.027).

Based on these results it was estimated that the fractionation sensitivity of breast cancer is around 4 Gy which is similar to that of the late reacting tissues.

UK START A: (22, 23)

START-A trial, the first of hypofractionation study in the UK was done across 17 centres from 1998 to 2002. The trial was designed based on data available from the pilot trial described above. One of the aims of the trial was to combine the data from this trial and the pilot study to arrive at a better understanding of the fractionation sensitivity of the breast tumors.

The trial included patients with pT1-3a and N0-1 disease who had undergone primary surgery and then required adjuvant radiation. The trial included patients who had breast conservation surgery and also those who had undergone mastectomy. 2236 eligible patients

were randomized to three different fractionation arms. The conventional regimen of 50 Gy in 25 fractions over 5 weeks was compared with the experimental regimens of 41.6 Gy in 13 fractions over 5 weeks or 39 Gy in 13 fractions over 5 weeks (Fig 3.8.1). All treatment schedules were delivered over 5 weeks so that treatment time duration will not be a factor in the final analysis. The regional lymphatics were included in the treatment field as per indication. The boost dose to the tumor bed was left up to the discretion of the treating centre.

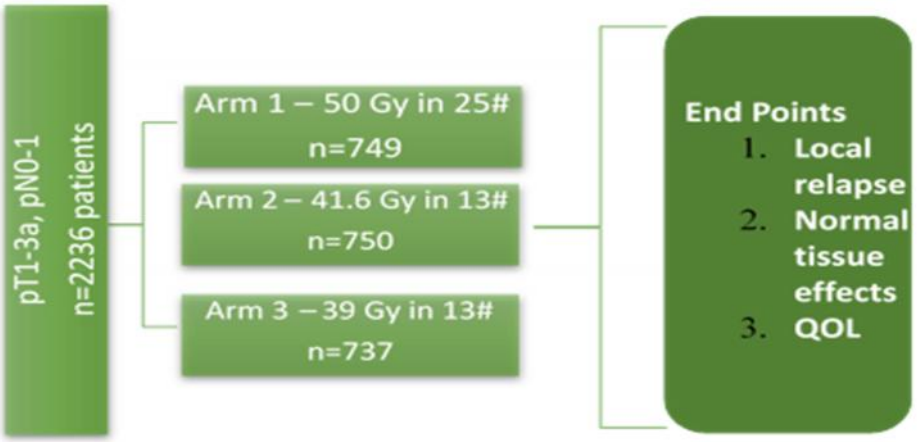


Fig 3.8.1: Trial Design of START A (# - fraction)

The primary end points of the trial were local relapse, normal tissue effects and the effect on the quality of life (QoL). Patients were followed up every year after radiation for locoregional relapse and normal tissue effects.

The trial was designed to detect 5% difference in the local relapse rates between the different radiotherapy schedules. At a median follow up of 9.3 years 6.2% of patients on the trial had locoregional relapse.

The locoregional relapse rate did not differ significantly between the 41·6 Gy and 50 Gy regimen groups (6·3%, *vs* 7·4%, hazard ratio [HR] 0·91; p=0·65) or the 39 Gy (8·8%) and 50 Gy regimen groups (HR 1·18; p=0·41). Breast size reduction and induration of the breast tissue were the most common side effects observed at the end of 10 years.

The incidence of moderate or marked normal tissue effects were significantly less in the 39 Gy group, whereas no significant changes were observed among 41.6Gy and 50 Gy group.

UK START-B: (24)

In the second of the parallel hypofractionated radiotherapy study, START B Trial, 2215 patients were randomized to two regimens comparing 40 Gy in 15 fractions of 2.67 Gy in 3 weeks with a control group of 50 Gy in 25 fractions of 2 Gy over 5 weeks.

The trial included patients with pT1-3a pN0-1 tumor after primary surgery requiring adjuvant radiotherapy (Fig 3.8.2). The trial was carried in 21 centres in the United Kingdom between 1999 and 2001. The inclusion of regional lymphatics in the irradiation field was based on clinical indications.

The delivery of boost radiotherapy to breast conserved patients was left to the discretion of the treating centre. Electron boost of appropriate energy delivering 10 Gy in 5 fractions was used for boost field radiation therapy. The primary end points in this trial were locoregional control, normal tissue toxicity and quality of life.

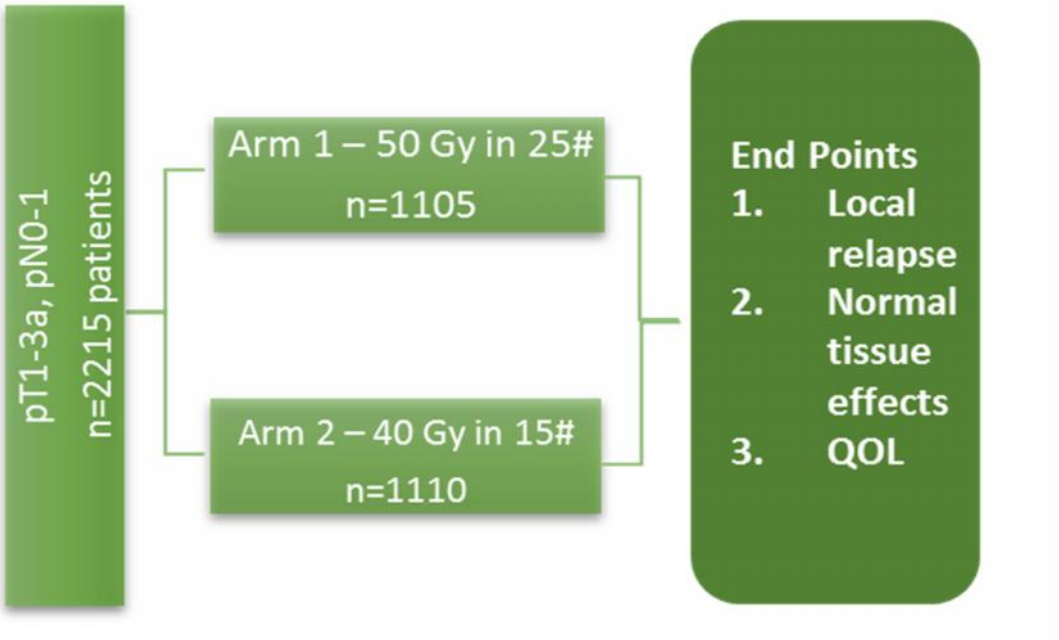


Fig 3.8.2: Trial Design of START B

1105 women were assigned to the 50 Gy group and 1110 to the 40 Gy group. The proportion of patients with locoregional relapse at 10 years did not differ significantly between the 40 Gy group (4·3%, 95% CI 3·2–5·9) and the 50 Gy group (5·5%, 95% CI 4·2–7·2; HR 0·77, 95% CI 0·51–1·16; p=0·21). At 10 years follow up the most common of the late effects were breast shrinkage and induration similar to the START A trial. All of the moderate to marked late normal tissue effects were significantly less common in the 40 Gy group than in the 50 Gy group.

In a combined post hoc analysis of the two START trials together and the pilot trial showed that the hypofractionation arms combined together did not vary significantly from the conventional fractionation with respect to control rates regardless of factors like age, type of surgery, stage of the tumor, grade of the tumor and this was also the same with respect to effects on the normal tissues.

CANADIAN TRIAL: (25)

Ontario Clinical Oncology Group carried out a randomized trial to find out the optimal fractionation regimen in adjuvant whole breast radiotherapy. 1234 patients who had undergone breast conservation surgery with negative margins and negative nodes on axillary clearance were randomized to two regimens. 612 patients were randomized to the conventional regimen of 50 Gy in 25 fractions over 5 weeks and 622 patients were randomized to 42.5 Gy in 16 fractions over 22 days.

The patients were stratified according to tumor size, systemic therapy, age and centre of treatment. The radiation therapy was delivered using tangential beams from Monday to Friday. The regional nodal regions (the axilla, supraclavicular fossa and the internal mammary nodes) were not included in the radiation portals. The patients in the trial did not get any tumor bed boost.

The primary endpoint in this trial was local recurrence and the secondary endpoints were regional and distant recurrence, late toxicities and cosmetic outcomes of the treatment and survival. After completion of the radiotherapy patients were followed up every 6 months. The first mammography was obtained 6 months after completion of the radiotherapy and then yearly during follow up. Late toxicities and the cosmetic outcomes of the treatment were assessed at 3, 5 and 10 years after completion of the treatment. The RTOG Late morbidity scoring criteria were used to assess the late skin toxicities and EORTC scale was used for assessing the cosmetic outcomes of breast conservation.

The cumulative incidence of local recurrence was 6.7% in the control arm compared to the 6.2% in the hypofractionated arm at a median follow up of 12 years. This is an absolute

difference of 0.5% with 95% confidence interval of -2.5 to 3.5. Hence the null hypothesis that the hypofractionated arm would be more than 5% worse than conventional radiotherapy was rejected on the basis of non inferiority ($p<0.001$).

Subgroup analysis also showed there was no effect of prognostic factors like receptor status, age, tumour size and the use of chemotherapy on the fractionation regimen. However high grade seemed to fare worse with hypofractionated therapy with local recurrence in control being only 4.7% compared to the 15.6% in the hypofractionated regimen in this subgroup. This was statistically significant ($p=0.01$). The probability of survival at 10 years follow up is 84.6 % vs 84.4 % favouring the hypofractionated regimen. However this difference was not statistically significant, $p=0.56$.

META ANALYSIS:

A meta-analysis from Cochrane Reviews published in 2010 (26) included four randomised trials mentioned above, which they described to be of low to medium quality. It analysed the effect of hypofractionation on local recurrence risk, breast appearance and survival at five years. The risk ratio (RR) for local recurrence was 0.97 (95% CI 0.76 to 1.22, $p=0.78$) and for survival at five years RR was 0.89 (95% CI 0.77 to 1.04, $p=0.16$). With regards to toxicity and cosmetic outcomes of the breast, the analysis showed that acute skin toxicity was significantly lesser with conventional fractionation ($p = 0.007$). As for the appearance of breast after radiation, the RR of 1.17 (95% CI 0.98 to 1.39, $p=0.09$) also confirms the superiority of hypofractionation regimens.

The results of the above described hypofractionated radiotherapy breast cancer trials are summarized in the following table (Table 3.8.1)

Table 3.8.1: Summary of the trials with hypofractionation

Study	No of patients	Median Follow Up	Treatment arms	End Point	Locoregional recurrence	Cosmesis
Royal Marsden Hospital/ Sutton and Gloucestershire Oncology Centre	1410	9.7 years	50 Gy in 25# 39 Gy in 13# 42.9 Gy in 13#	Late changes in breast appearance	After 10 yrs 12.1% 14.8% 9.6% (p of 39 vs 42 Gy = 0.027)	50 vs 39 p =0.01 50 vs 42.9 p =0.05
UK **START A**	2236	9.3 years	50 Gy in 25# 41.6 Gy in 13# 39 Gy in 13#	Loco-regional tumor recurrence	50 vs 41.6Gy HR=0.91 50 VS 39 HR=1.18	------
UK **START B**	2215	9.9 years	50 Gy in 25 fx 40 Gy in 15 fx	Loco-regional tumor recurrence	5.5% HR-0.77 4.3%	Late effects (Induration and breast shrinkage) were similar
Ontario Clinical Oncology Group	1234	12 years	50 Gy in 25 fx 42.5 Gy in 16 fx	Local recurrence	6.7% Vs 6.2%	Similar in both arms

3.9 EXTREME HYPOFRACTIONATION:

The encouraging results of the previously described hypofractionated radiotherapy trials, inspired people to experiment with further hypofractionation regimens.

The UK FAST trial is one such trial. It randomized 729 eligible patients to three arms comparing 50 Gy in 25 fractions and 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6.0 Gy, respectively, was given to the whole breast. The objective was to assess the 2-year change in photographic breast appearance. The early results published concluded that at the end of 3 years of median follow up, it was found that 28.5 Gy is comparable to the conventional 50 Gy and it is significantly milder with regard to adverse effects than 30 Gy (27). This trial shows the extreme hypofractionation may be possible to an extent.

3.10 CONTROVERSIES WITH HYPOFRACTIONATED RADIOTHERAPY

ALPHA/BETA RATIO:

The alpha beta ratio of any particular tumour is a numerical representation of the fractionation sensitivity to radiotherapy. Outcome data from several clinical trials of breast cancer were used by Qi et al, to develop a model which was based on linear quadratic (LQ) model and Poisson model to calculate the alpha beta ratio of breast cancers. The linear quadratic parameters were used to propose hypofractionated regimens. The analysis of the available data helped to arrive at a conclusion of an alpha/beta ratio of 3.89+/-6.25 Gy. With this low alpha beta ratio the following regimens are equivalent to the conventional regimen of 2.0Gyx25 in 5weeks: 2.26Gyx20, 3.34Gyx10 and 4.93Gyx5 (28).

Further in the analysis of the locoregional relapse from the START A trial, the alpha beta ratio was derived to be around 4 Gy with 95% CI from 0 - 8.9 after adjusting for all the prognostic factors. Also a meta-analysis of the START trials and the pilot study also confirmed a low alpha beta ratio of around 3.5 Gy with 95% CI of 1.2–5.7 (23). This confirms the fact that though hypofractionation in breast cancer treatment was started off more empirically than based on real evidence, it does have strong radiobiological basis.

3.11 GRADE AND HYPOFRACTIONATION:

In the Canadian trial it was noted on subgroup analysis that the grade of the tumor was a significant factor for the fractionation sensitivity of breast cancers. In an author reply to this analysis by Whelan et al (25), Yarnold et al (29) did a small meta-analysis of three trials including START A, START B, and the Canadian study to test this hypothesis. The locoregional relapse rates was 4.9% in the patients on the conventional regimen compared to the 5.2% on the combined hypofractionation arms. The three trials combined had 4833 patients on whom details of the tumor grade was available for analysis.

The hazard ratio for locoregional relapse of the hypofractionated regimens combined together was 1.28 for grade 1 and 2 tumors and was 0.83 for grade 3 tumors. This result was not statistically significant, $p=0.12$. The α/β values were estimated to be 3.6 Gy (95% CI, 0 to 7.4) for grade 1 and 2 tumours and α/β was 2.2 Gy (95% CI, 0 to 5.5) for grade 3 tumors. Although the difference in α/β values seems to be large the CI is overlapping for all grades of tumor. This may be accounting for the non significance of the tumor grade on fraction size.

3.12 POST MASTECTOMY RADIATION THERAPY:

All of the randomised trials discussed above have not specifically looked at post mastectomy patients getting hypofractionated radiotherapy. In a trial from Egypt, 107 patients who had mastectomy and adjuvant radiotherapy were randomised to three arms of 50 Gy in 25 fractions, 45 Gy in 17 fractions versus 40 Gy in 15 fractions. Although grade 2-3 erythema was significantly more in case of hypofractionated arms, there was significant difference in the local control rates (30). Similarly pain, fibrosis, arm oedema and pigmentation were also not significantly different in the three arms.

Another randomised trial from Pakistan compared three different fractionation regimens in locally advanced breast cancer patients following mastectomy. The three arms were 40 Gy in 15 fractions, 27 Gy in 5 fractions and 35 Gy in 10 fractions. The study assessed differences in local control, toxicity and workload between the three arms. Except for the difference in the skin toxicities, all the other factors did not show any statistically significant difference in the three arms (31).

GUIDELINES ON POST MASTECTOMY RADIOTHERAPY:

- The recommendations for PMRT are T3N1,T4N1,T4N2 and T1-2 tumours with 4 or more positive nodes
- In patients with T1-2 disease with 1-3 lymph nodes, there is some controversy regarding the benefit of PMRT.
- There is significant locoregional control in patients with pT3N0, though there is questionable benefit regarding the survival.

- Patients who received neoadjuvant chemotherapy followed by mastectomy, it is mandatory to deliver PMRT if the initially stage was III or residual nodal involvement.

The American society for radiation oncology (ASTRO) constituted a task force in 2011 to devise recommendations for hypofractionated radiotherapy in early breast cancers (32). They concluded that there was enough evidence to state that hypofractionated radiotherapy is equivalent to conventional radiotherapy albeit with certain caveats. The committee recommended certain criteria to consider patients for hypofractionation.

Also it was suggested that 42.5 Gy in 16 fractions is a favourable dose schedule and that heart should be excluded from the treatment because there is a lack of mature data on the safety of cardiac tissues in hypofractionated radiotherapy. The committee felt for the patients who do not meet all the aforementioned criteria the evidence is not good enough to recommend hypofractionation, as these kind of patients are not represented well enough in the randomised trials or are not mentioned in the subgroup analysis of these trials.

The ESMO guidelines for the management of invasive breast cancer published in 2012 (33) suggests that hypofractionated radiation therapy is an alternative to the standard conventional fractionation. Their favoured dose schedule in that case is 42.6 Gy in 16 fractions. They advise caution in the case of grade 3 tumors, young patients, post mastectomy patients and in those patients in whom regional radiotherapy is warranted.

NCCN guidelines of 2013 also state the use of 42.6 Gy in 16 fractions as equivalent to 50 Gy in 25 fractions in the setting of whole breast radiotherapy. But the dose guidelines for the regional lymphatics mention only conventional fractions of radiotherapy to 50 Gy. Interestingly there is no mention of dose fractionation in the section on post mastectomy radiation therapy.

3.13 ACCEPTANCE OF HYPOFRACTIONATION IN INDIA

Indian literature on hypofractionated post mastectomy radiotherapy is limited. In a study conducted between 1989 to 1992 by **Goel et al** (36) compared two radiotherapy schedules, 40 Gy in 17 fractions (2.35 Gy per fraction) over 3.2 weeks and 45 Gy in 20 fractions (2.25 Gy per fraction) over 4 weeks in patients who have undergone modified radical mastectomy. Cobalt 60 unit was used for the treatment. Chest wall failure was noted in 10% and 5.6 % of patients in the first and second treatment groups respectively. Skin reactions, which were reversible, were the commonest side effect in both the groups. This study concluded that, both these shorter fractionation schedules are equally efficacious and tolerable for the Indian women.

Another retrospective study from **Post Graduate Institute Chandigarh(35),** published in 2007, assessed 688 patients who had post mastectomy radiotherapy between 1995 and 2000. The schedule used was 40 Gy in 15 fractions using Co 60. The five year local control was 94.4 % and frequency of locoregional recurrence was 8.5%. The incidence of WHO Grade III dermatitis was 7.1% and acute pneumonitis was seen in 3% of patients.

A recent practice survey which looked into patterns of locoregional treatment (2006 - 2008) in breast cancer conducted by Tata Memorial Hospital, published in 2010, reported that 67% of Radiation Oncologists approved the standard 50 Gy in 25 fractions schedule for patients with early breast cancer, after breast conservation surgery. Another 23% of doctors preferred 45 Gy in 25 fractions and surprisingly none of them approved hypofractionated radiotherapy. The questionnaire in that survey gave five different schedules and the most common schedule (82 %) was 50 Gy in 25 fractions (34).

These studies suggest that eventhough hypofractionated radiotherapy was being practiced in our country from as early as 1989; there is still paucity in whole hearted acceptance of this shorter radiotherapy schedule. One of the reasons might be the lack of availability of Three Dimensional Conformal Radiotherapy facilities across the country, which is safer in delivering this higher dose per fraction.

Another hurdle in applying this regimen in our country is the limited finances of our patients which precludes 3DCRT for them. Then, among the affordable patients, there is a tendency to assume that the longer treatment schedule would benefit them more in terms of recurrence of cancer. When informed about the higher dose per fraction, there is a fear among some patients regarding higher chance of side effects.

Breast cancer patients form a major proportion of patients being treated in our Institution and many of them are able to afford 3DCRT. Even though there is robust evidence for safety and efficacy of hypofractionated radiotherapy, our Institution was continuing the longer (46-50 Gy in 23-25 fractions) schedule. With the increase in breast cancer patients, the load on the Linear accelerator also increased and hence we proposed this study to look into the feasibility of changing over to the shorter regimen for eligible patients.

3.14 ECONOMIC BURDEN OF CANCER THERAPY:

HIGHLIGHTS OF AMERICAN CANCER SOCIETY:

- Disability from cancer and the total economic impact of premature death was estimated in 2008 to be $895 billion. The direct treatment costs which was not included in this analysis was around 1.5% of the world's GDP.

- The global burden of cancer was estimated using a formula accepted by the public health researchers and economists and was found that 83 million years ($ 188 billion), colorectal cancers($99 billion) followed by breast cancers ($ 88 billion).

- Across the world, cancer causes thge highest economic loss among the top 15 leading causes of death.

- Cancer is responsible for the highest economic toll (20 % more than for heart disease) followed by heart disease which is the second cause.

"Financial toxicity" is an adverse event of any type of cancer therapy. More and more attention is being paid to the financial toxicity of cancer treatment. An adverse effect of financial toxicity is that a significant number of patients take less than the prescribed amount of medication or avoid medication altogether (37). In a country like India, these people may be pushed towards cheaper alternatives like traditional medicine, the efficacy of which in cancer care is not really known. Standard treatment at affordable cost may prevent these patients moving towards cheaper alternatives.

Further the reduction in duration also helps in better utilisation of available resources. This is particularly imperative in a country like ours where the cancer treatment centres are woefully under resourced to cater to the huge volume of patients.

Economic analyses can be applied to a common clinical condition where two alternative management can be used with substantial financial benefit. Economic evaluation assesses the expenses for a treatment that can achieve a measurable health outcome, like number of years of life gained. Economic analysis can be useful for planning and developing a breast cancer control policy, to guide budget development and to allocate scarce resources to National Cancer Control Programs.

However there is a dearth of economic evaluations of breast cancer radiotherapy in literature**. Barbieri et al (38**) in a study in UK searched the literature for studies assessing the economics of radiotherapy in breast cancer. They concluded that there is a lack of evidence on the cost effectiveness radiotherapy in cancer to support decision making in the United Kingdom.

Few of the studies assessing the cost effectiveness in breast cancer treatment with radiotherapy are elucidated below.

Sen et al (39) analysed the cost effectiveness of radiation therapy in elderly female patients with favourable risk breast cancer. They concluded that EBRT is cost effective for elderly women but did not have any susbstantial benefit in patients with shorter expected survival. Alvarado et al (40) analysed the cost effectiveness of intraoperative radiotherapy in breast cancer and concluded that apart from the need for finances in the initial process of setting up the unit, the practice of IORT is cost effective in early breast cancer treatment.

Cost comparison analysis for various radiation modalities after lumpectomy for early breast cancer is available. Greenup et al (41) analysed the radiation modalities needed for the patients by a cost minimization strategy. It was shown that by receiving the cheapest modality that the patient was eligible, the radiation cost was reduced by US $ 5.69 million per

1000 patients treated which amounted to a 43 percent reduction from what would have been spent had all patients received the same treatment of whole breast irradiation.

The cost effectiveness of fractionation in breast cancer has been analysed by a few (42,43**). Dwyer et al** assessed the impact of hypofractionated radiotherapy in breast cancer on cost and hospital waiting time in a hospital in Australia where it is not the standard regimen. He concluded that had all patients been treated this way, extra 14 patients would be treated each month and also the cost would have been reduced by 24% (41).

3.15 ECONOMIC EVALUATION :

Evaluation of the economics of two alternative intervention is the formal comparison, in aspects of resources as well as clinical outcome generated. The results of these economic evaluation are expressed in terms of incremental cost effectiveness ratios and cost per quality adjusted life year or per life year gained.

Economic evaluation deals with costs and effectiveness of an intervention. Well documented clinical evidence for the intervention is essential. Most important step in economic evaluation is that alternatives to be compared are defined. Economic evaluation should take into considerations the costs and consequences of alternatives.

Economic evaluations are distinguished by the outcomes of the comparable alternatives are measured. Economic evaluation are classified into four categories namely : cost minimisation, cost effectiveness, cost utility and cost benefit analysis (Table 3.15).

Method of analysis	Measurement / assessment of costs	Measurement / assessment of outcome	Cost-outcome comparison
Cost-minimisation analysis (CMA)	Monetary	None	None
Cost-effectiveness analysis (CEA)	Monetary	Natural units	Costs per outcome unit
Cost-utility analysis (CUA)	Monetary	Utility values	Costs per QALY
Cost-benefit analysis (CBA)	Monetary	Monetary	Net costs

Table 3.15.1: Classification of Economic evaluation

COST-MINIMISATION ANALYSIS

This analysis compares the net costs of two or more therapeutic alternatives with the same effectiveness or efficacy. This analysis helps to establish the cheapest alternative. The equivalence in efficacy of the comparators are presented comprehensibly and transparently.

COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness analysis expresses the costs in monetary units and the results in non-monetary units. Non-monetary units, for example be: (1) hospital days prevented, (2) years of life gained, (3) clinical parameters (e.g. response or remission rates, etc).

COST-UTILITY ANALYSIS

The same principle of cost-effectiveness analysis holds for cost-utility analysis. This analysis expresses costs in monetary units and the benefit as a non-monetary unit. This concept merges quality of life and life expectancy. This measure of analysis should be chosen when quality of life is considered as an important aspect of therapy.

COST-BENEFIT ANALYSIS

Assessesment of all effects, especially health effects, in monetary units are done by cost benefit analysis. The limitation in this analysis is that a monetary assessment of clinical results must be made even though methodologically this is difficult to perform. This method of analysis is not used due to these methodological limitations.

COST DETERMINATION

Basically, all costs pertaining to the chosen study must be assessed and included in the analysis. In health economics, costs are defined in terms of the economic means and understood as the financially quantified consumption of resources.

Direct costs attribute to all utilization of resources as a result of therapy and directly contribute to this. Direct costs comprise direct medical and non-medical costs. Those expenses that arise directly from the treatment are direct medical costs (e.g. diagnosis, drug therapy, medical care, in-patient treatment, etc). Non-medical costs are those that arise from the effects of the disease or treatment (e.g. transport costs, care services, etc.).

Consumption of resources occurring not in direct relation to the treatment of the disease are quantified as **Indirect costs**. This comprises loss of productivity resulting from premature death and illness. Measurement of Indirect costs is essential if impairment of capacity to work and the absence from the workplace is to be considered together.

Losses of productivity are expressed by the **human capital approach**, i.e. the time duration related income of the concerned patient group. Mean values can be used from official statistics when no specific data are available for the patient group.

$$\textit{Loss of productivity} = \textit{Incapacity for work} \quad x \quad \left\{ \frac{\textit{Wage costs}}{\textit{Dependent employees x 365 days}} \right\}$$

Components of Out-of-Pocket Costs[a]

TYPE OF COST	DEFINITION	APPLICATION TO THIS STUDY
Direct costs	Costs associated with medical services that are typically reimbursed (at least in part) by third-party payers; a subset of these costs are borne by the patient	Direct medical + direct nonmedical costs
Direct medical costs	The cost of medical resources consumed, such as physician visits, surgery, medical supplies, and hospitalization; includes medical professional time; may also include costs borne by the patient, such as certain household expenditures (eg, home assistance or special equipment), special diets, and clothing; includes some time costs	Hospital bills, physician visits, medications, medical second opinion, experimental treatment, visiting nurse/home health aid, prosthetics, counseling, nutrition supplies, physical/speech therapy, special equipment, herbal remedies, alternative therapy[b]
Direct nonmedical costs	The cost of nonmedical resources, such as childcare or transportation, attributable to treatment (eg, transportation for medical visits)	Childcare, transportation, restaurant meals, phone calls, hotel stays, housekeeping
Indirect costs	The value of economic resources, including wages or other income lost due to disease-related disability or premature mortality, as well as unwanted job changes	Lost income
Indirect nonmedical costs	The value ascribed to time lost from work, housekeeping, etc, by family members or friends who transport, visit, and care for patients	Caregiver survey

Table 3.15.2: Table showing the different types of cost/components of out of pocket costs (Financial Burden of cancer : Estimates from a study of women with breast cancer- Arozullah et al)

3.16 ECONOMIC STUDIES IN INDIA:

A recent study conducted at the All India Institute of Medical Sciences (AIIMS), New Delhi (2011analysed about the mean cost of radiotherapy. 59% of this spent on the direct non medical costs like food, transportation and accommodation and 41% is spent on the direct medical costs that is treatment specific costs.(44)

Mahal et al. (2010) showed that almost 50% of households having a member with cancer experiences catastrophic spending and 25% are driven to poverty by health care costs.(45)

3.17 OUTCOME PARAMETERS :

The following outcome parameters can be chosen:

Economically directed outcome measures like number of days of hospitalization, days of incapacity for work, etc.

Clinical outcome parameters – This includes biochemical or physiological, morbidity- or mortality-related parameters. Three end points are used as a measure of outcome. They are :

- Final endpoints
- intermediate endpoints and
- surrogate endpoints

Health-related quality of life is considered as the outcome indicator in specific indications - particularly where the medical treatment does not contribute to the prospect of either a cure or a significant prolongation of life.

3.18 NEED FOR ECONOMIC ANALYSIS:

Health policy of a nation especially should address on the access, quality and cost of the health care. A 'free market' of medical care relies on the notions of "perfect information" and "perfect competition". Yet, the awareness of financial impact of the disease does not prevails among the people. Cancer is one such disease that brings greater stress for patients and families due to the financial burden of treatment. Substantial section of income and family budget are lost due to the out-of –pocket costs incurred. However, a good estimate of the expenses involved is lacking in part of patients and their family. This is the reason of concern about health policies, even in developed countries like UK and USA.

Alternative management strategies may have feasible financial effects that make economic analyses appropriate. People may consider radiation therapy to be expensive, especially in the post mastectomy setting, where complex treatments essential to deliver multiple fields administered.

The expense of such modality of therapy may be justified by robust cost-effectiveness analysis. The 58th World Health Assembly in May 2005 (46), has acknowledged the increasing burden of breast cancer in its resolution on cancer prevention and control. Therein, member states are intended to reinforce or to develop comprehensive cancer control programs to reduce cancer related mortality and to enhance quality of life for patients and their families.

Information on reinforcement of planning or developing a breast cancer control policy is best provided by economic analysis. This economic analysis can guide budget development, justify allocation of scarce resources to national cancer control programs. This analysis can contribute to identify the efficient ways of delivering diagnostic and treatment services. Earlier most of such economic analysis involving the costs and health effects of

breast cancer control interventions were performed in developed countries. But information to guide decisions in resource allocation is lacking in developing countries. Moreover, studies have largely ignored interactions among interventions, rather they focused on individual interventions. Moreover, majority of studies have been performed on places where breast cancer care was already existed, instead focusing on situations where they barely needed it. This limitation precludes comparisons with interventions in settings where care systems have not been established or with interventions that might be more relevant to other regions of the world.

Earlier studies have shown that modest increase in fraction size when combined with appropriate downward adjustments to total dose in post mastectomy setting has satisfactory outcomes in terms of tumor control and late adverse effects. Reduction in duration of therapy lessens the financial burden on the family and indirectly helps in delivering care to more individuals. It also helps in better utilization of available resources.

3.19 RADIOTHERAPY COST STRUCTURE: INSTITUTION PERSPECTIVE

The main reason for the rise in health care expenses is the rapid evolution in medical technology and its developments. Radiation oncology is highly technological discipline which includes many developments in the treatment delivery.

But the cost consequences of the technical advances remain is yet to be explored and evaluated. The most crucial determinant of radiation oncology is the equipment costs which is highly expensive that also demands sound infrastructure and high level maintenance. The advanced treatment planning and delivery systems in radiotherapy is also labour intensive. The third determinant is that as the complexity of treatment increases, the resources utilized in terms of person, place and time will be more and hence adds to the total cost(42).

The cost of radiotherapy is calculated by the treatment time which is the daily treatment time multiplied by the number of fractions. Inversely, we can conclude that decrease in the daily treatment time or decrease in the number of fractions can result in cost containment.

3.20 NON MEDICAL COSTS OF THE PATIENT:

In a broader perspective, to reflect the societal aspect, an American analysis calculated the non medical costs which accounted for 8- 25% of the total costs. It includes the expenses for transportation and time spent on the treatment which was multiplied with the average hourly wages of the breast cancer patients. It was obvious that there was link between the number of fraction and nonmedical costs in terms of expenses towards travel, time and loss of productivity.

3.21 RADIATION TOXICITY

The benefits of local control and overall survival provided by post mastectomy radiotherapy are associated with certain side effects. The organs at risk (OAR) in post mastectomy radiotherapy are the skin, subcutaneous tissue, ribs, lungs, heart, spinal cord and the contralateral breast.

Radiation induced damage can be influenced by certain patient and treatment related factors. Patient related factors like obesity being associated with higher risk of skin toxicity, co morbidities like diabetes mellitus, connective tissue disorders, cardiac diseases and previous history of smoking also could have a detrimental effect on the toxicity profile. The treatment related factors like the energy chosen, the technique applied, dose prescribed and

the treatment plan also can have an impact on the radiation induced damage. The dose delivered per fraction and the total duration of therapy will influence the toxicity of therapy

Toxicities can be classified as early and late effects. Early effects occur during the course of radiation therapy and upto six months post treatment. Late effects may occur from six months to years after the treatment. The acute side effect which is most commonly encountered is fatigue and irritation of skin. Fatigue is usually mild and does not affect the activities of daily living. Some form of radiation dermatitis occurs in most of the patients (90%) receiving post mastectomy radiotherapy. Radiation induces injury in the basal stem cells that are responsible for replenishing the superficial cornified layer of the epidermis (Fig: 8). As a result of the insult to the basal stem cells, there is shedding of the cornified layer eventually, which is termed as dry desquamation.

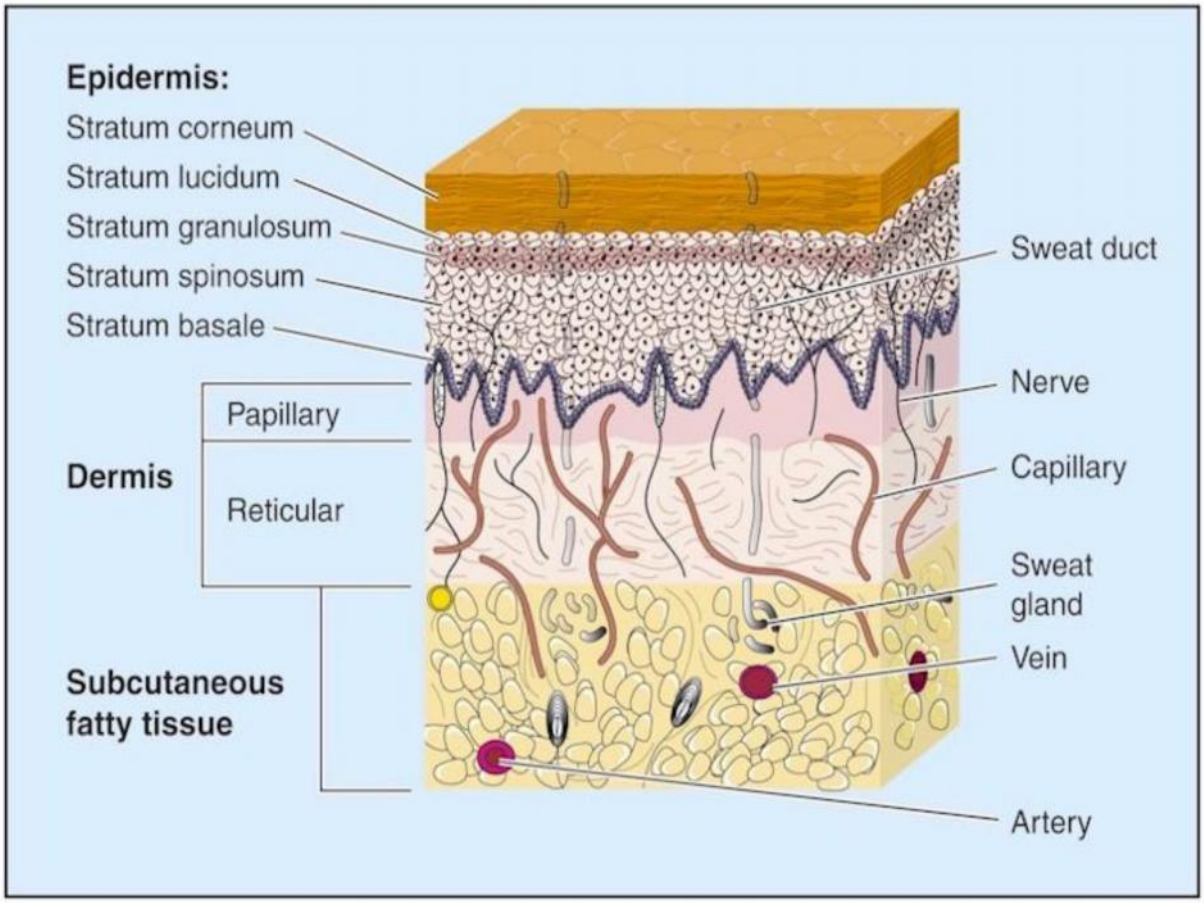


Fig: 3.21.1: Layers of skin

Radiation also causes dilatation of capillaries, increased vascular permeability, enhanced inflammatory response leading to erythema and oedema. Hyperpigmentation, epilation, loss of sebaceous glands and sweat glands are all part of radiation dermatitis, resulting in dry and pruritic skin. Migration of the melanocytes from the basal layer to the superficial layers causes hyper-pigmentation. Moist desquamation occurs with continued loss of basal layer which exposes the dermis. Moist desquamation can lead to frank ulceration.

A study from Egypt, which looked into radiation dermatitis in conventional radiotherapy and hypo-fractionated radiotherapy in conserved breasts, reported that the peak incidence of severe skin reaction occurred during the fifth week of treatment in the conventional group and in the third week in the hypo-fractionated group. The study also reported that these reactions lasted for about three weeks in the conventional fractionation group and for five weeks in the hypofractionated arm (45).

The explanation for the early incidence of reactions in the hypofractionated group may be the dependence of timing and magnitude of inflammatory response on the rate of accumulation of dose. Inflammatory response does not clear up in hours like the sublethal damage do and hence the inflammatory response accumulates quickly (47). START B trial analysed patient self-assesments of five key normal tissue effects on the breast and chest. This analysis showed that rates of moderate or marked changes were lower in the hypofractionated radiotherapy group compared to the conventional arm (48).

The various normal tissue effects like breast shrinkage, hardness, change in skin appearance, swelling in the area of affected breast at five years were all consistently in favour of the 40 Gy in 15 fractions regimen.

An unusually marked acute skin reaction occurred in 16 (0.7%) patients in the START B trial. Of these 16 patients, 13 (1.2%) were in the conventional fractionation group and 3 (0.3 %) were from the study arm. Radiation dermatitis is graded based on the RTOG Acute Radiation morbidity scoring criteria (49).

GRADE	0	1	2	3	4
SKIN	No change over baseline	Follicular/faint /dull erythema epilation, dry desquamation decreased sweating	Tender/bright /bright erythema, patchy moist desquamation, moderate edema	Confluent moist desquamation, other than in skin folds, pitting edema	Ulceration, hemorrhage, necrosis

Table 3.21.1: RTOG Acute Radiation Morbidity Scoring Criteria

Radiation pneumonitis typically occurs as a late effect and may present with low grade fever and dry cough. Interstitial inflammation is the hallmark of radiation pneumonitis. Several patient and treatment related factors are associated with radiation pneumonitis.

Cardiac toxicity can also occur as late toxicity and is there is likelihood of its incidence in left sided breast cancers. **Lymphoedema** is the abnormal swelling of the arm which may occur after modified radical mastectomy or more commonly as a sequel of both surgery and adjuvant radiotherapy to the axilla. The highest rate of lymphoedema is seen in patients who undergo complete axillary dissection (levels I-III) followed by axillary irradiation.

Materials and Methods

4. MATERIALS AND METHODS

This is a prospective study conducted in Dept of Radiotherapy, Christian Medical College (CMC). CMC provides services to a large number of patients from in and around Vellore and surplus patients from the Eastern parts of our country. Patients who required Radiotherapy after Modified Radical Mastectomy or adjuvant chemotherapy were included in the study.

Study design:

This is an economic evaluation study. A cost minimisation analysis was done for the two groups as the outcome for the two groups would be the same as known from the randomised trials of Hypofractionated radiotherapy.

Inclusion and Exclusion criteria

INCLUSION CRITERIA:

- Age 18 to 70 years
- All patients receiving conventional post mastectomy radiation therapy

EXCLUSION CRITERIA:

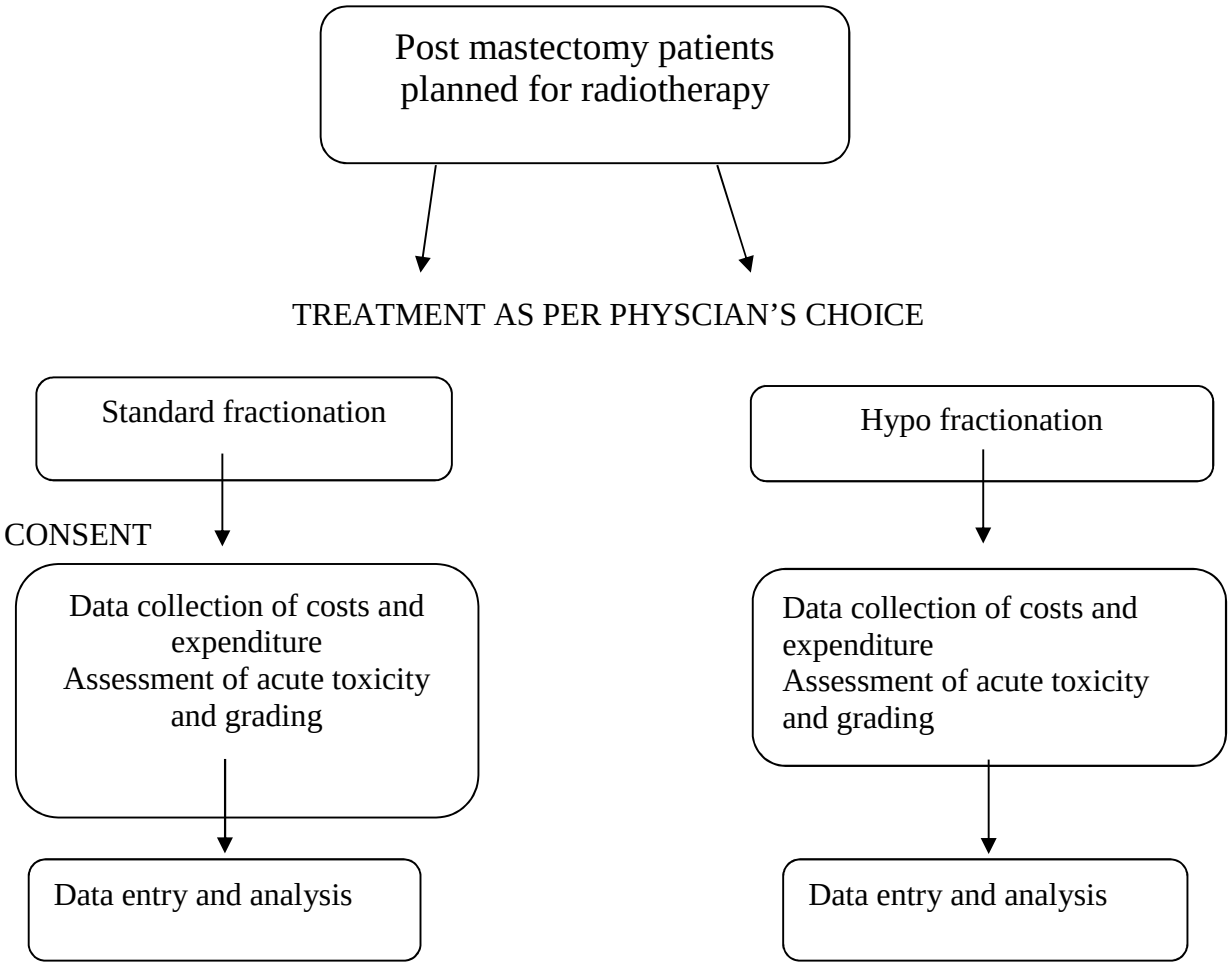
- Patients not willing to maintain a diary for this study
- Patients who had breast conservation surgery
- Patients receiving conformal radiotherapy

The proposed study was presented in the Institutional Review Board (IRB) which includes Research committee and Ethics Committee and approval was obtained (copy enclosed). The patients were selected based on the inclusion and exclusion criteria from among the invasive breast cancer patients after mastectomy into standard or hypo fractionated radiation therapy.

4.1 STUDY DESIGN:

This is an economic evaluation study. A cost minimisation analysis was done for the two groups as the outcome for the two groups would be the same as known from the randomised trials of Hypofractionated radiotherapy

Detailed diagrammatic Algorithm of the study



SAMPLE SIZE:

This study group consisted of 30 patients seen in the Radiation therapy department from February to August 2014, treated with standard fractionation and hypofractionated post mastectomy radiotherapy by conventional technique meeting the eligibility criteria were included in each arm.

Post mastectomy patients who came to the Dept of Radiotherapy after adjuvant chemotherapy were assessed. Some of the patients might have been already started on hormonal therapy. Those patients who had indications for PMRT were discussed about the need, costs, duration, benefits and side effects of radiotherapy. Those patients who opted for conventional radiotherapy are included in the study.

They were advised to review with basic blood investigations like complete blood counts, Serum creatinine, and liver enzymes. Ultrasound abdomen screening was also done for metastatic work up before initiation of radiotherapy in locally advanced carcinoma breast patients.

4.2 RADIOTHERAPY PLANNING:

The patients were planned for external radiation therapy as follows-

1. Immobilisation:

The patient were positioned on the simulation couch in supine position with the arm abducted (90 degree or greater) and head turned to the contralateral side on a breast board in stable and reproducible manner. Unilateral arm pole was used for immobilisation. A triangular wedge was inserted under the shoulder to correct the slope of the chest wall and to ensure that the sternum was parallel to the couch.

These measures are done to decrease problems arising with field matching between the tangential and supraclavicular fields. It was made sure that the arm was not in the path of the tangential beams and nodal regions could be treated without any difficulty.

Fig 4.2.1 : Immobisation of the patient

2.Planning Process:

After the patient was setup in the treatment position, the laser alignment system was used make sure that the patient was in straight position and the patient's midline was marked.

4.3 RADIATION THERAPY TECHNIQUES

The volume of irradiation includes the chest wall and the drainage lymph nodes when indicated.

Radiation Portals:

The portals used for irradiation are two tangential beams for the chest wall, a direct supraclavicular field including the axilla when necessary and internal mammary chain boost when required

Chest wall portals -Tangential Fields

Medial border: 1cm across the midline on the contralateral side. Additional dose may be needed to adequately treat the Internal Mammary Nodes.

Lateral border: aligned with mid axillary line or if the surgical scar extends beyond mid axillary line, it is kept such that the scar is treated with adequate margin.

Superior border: abuts the lower border of the supraclavicular field.

Inferior border: extends along the chest wall to include the infra mammary fold or atleast a 2cm margin on the scar.

Fig.4.3.1: Patient in treatment position for tangential field

Supraclavicular Portals:

The Supraclavicular portal is positioned with the inferior border at the first or second intercostal space 2-4 cm below the suprasternal notch. The medial border is at the midline, extending upward and following the medial border of the sternocleidomastoid muscle to the

thyrocricoid groove. The lateral border is at the medial end of head of Humerus and the superior border is at the level of the thyroid notch. The larynx is shielded.

Fig 4.3.2: Patient with external markings for supraclvicular and tangential fields

Supraclavicular and Axillary Portals:

Direct Anterior field:

Direct Anteroposterior Field

The Supraclavicular portal is positioned with the inferior border at the first or second intercostal space 2-4 cm below the suprasternal notch. The medial border is at the midline, extending upward and following the medial border of the sternocleidomastoid muscle to the thyrocricoid groove. The lateral border appears as a vertical line at the level of the anterior axillary fold. The superior border is at the level of the thyroid notch. The larynx and the head of humerus are shielded.

Direct Postero Anterior Axillary Field

Medial border is along the convex lateral wall of the bony thorax and 1 to 1.5cm of peripheral lung.

Medial Superior border is along the spine of scapula.

Lateral Superior border bisects the head of humerus.

Lower lateral border is medial to the border of Lattissmus dorsi.

Inferior border matches the lower border of the supraclavicular field anteriorly with not more than 1cm overlap as seen in treatment position.

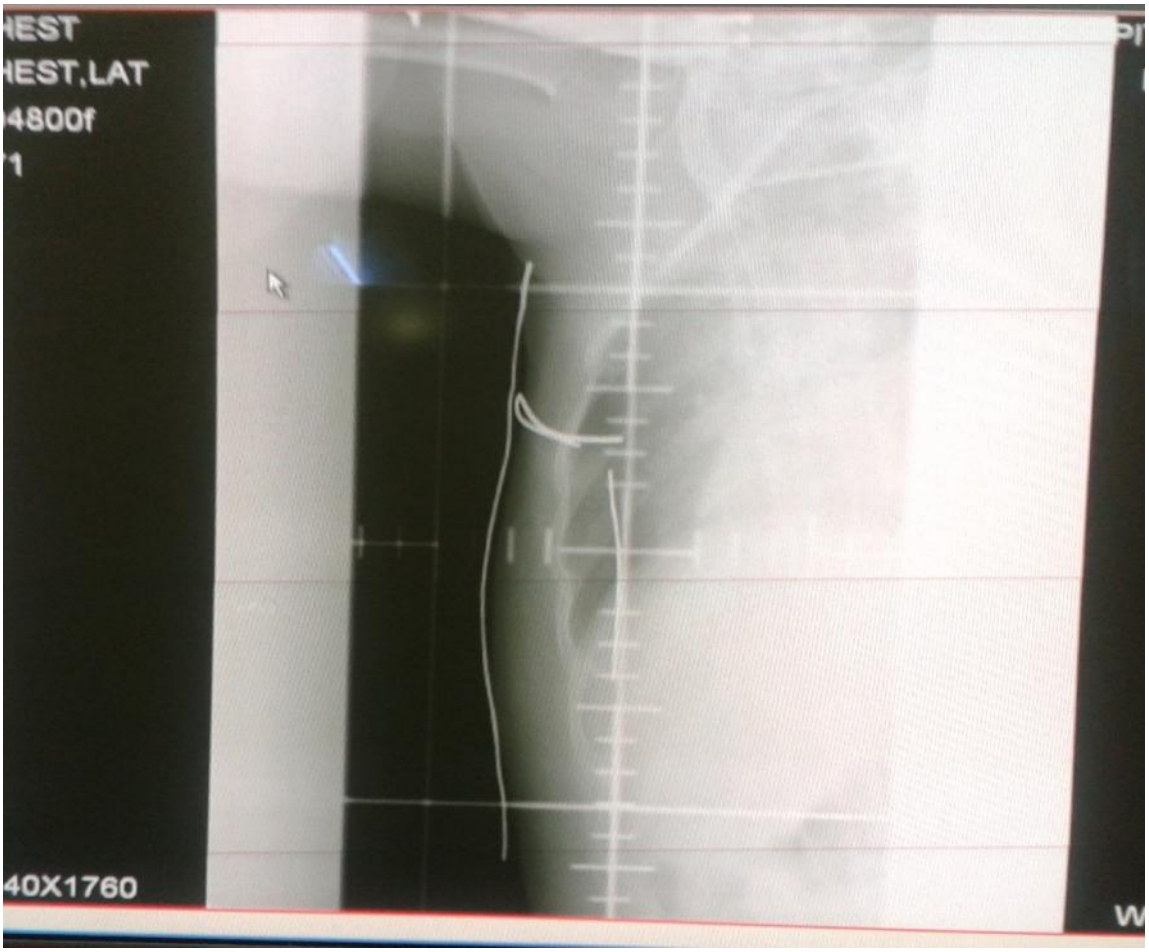


Fig 4.2.3 : simulation film during planning to measure the lung distance

After simulation, planning is done in the treatment planning system and appropriate plan is finalised by the oncologist

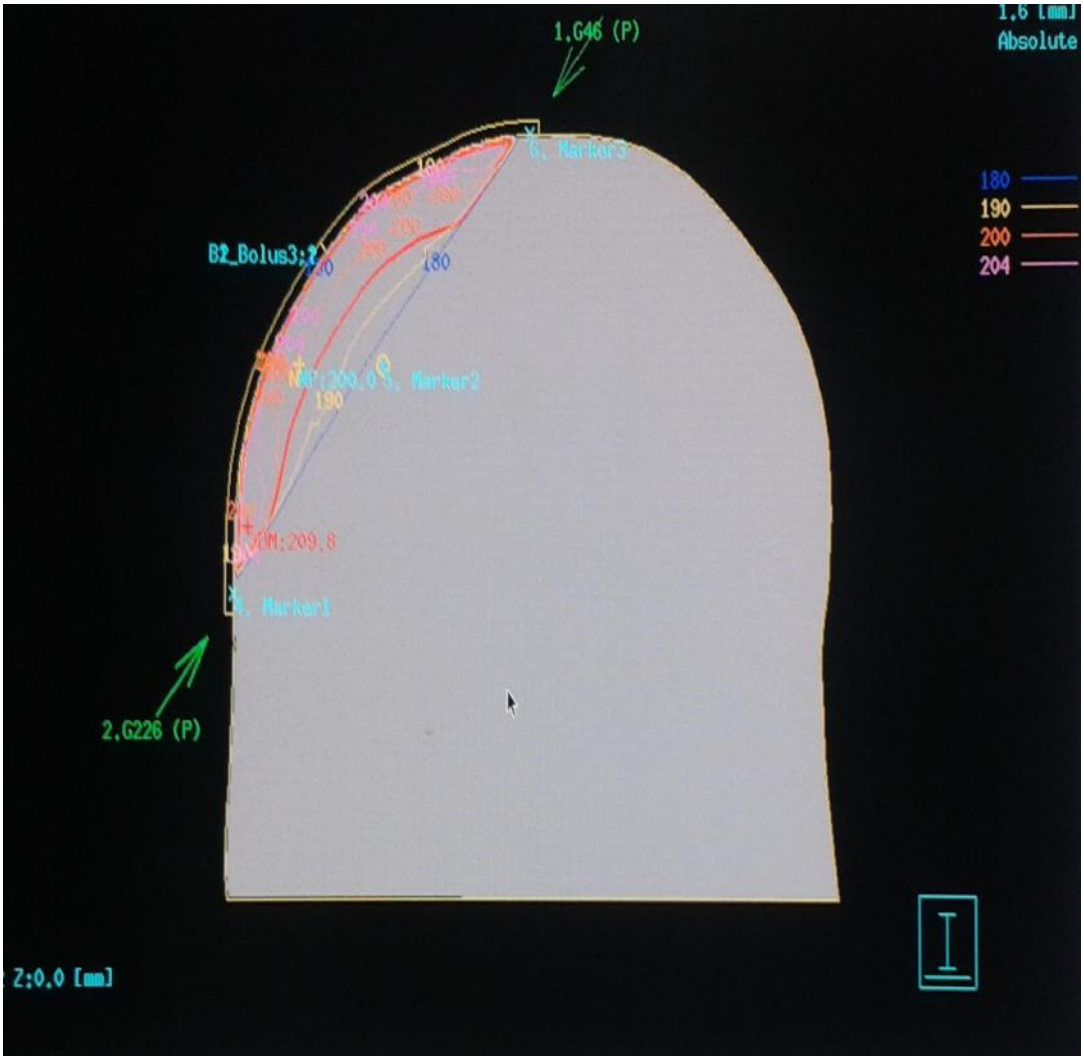


Fig 4.2.4 : Image showing isodose distribution in treatment planning system

Region treated	Energy used	Dose prescription	Duration
Chest wall	Cobalt/ 6 MV	50 Gy in 25 fractions Or 40 Gy in 15 fractions to tumour volume	5 days a week for 3weeks/ 5 weeks
Supraclavicular region	Cobalt/ 6 MV	50 Gy in 25 fractions Or 40 Gy in 15 fractions to 3 cm depth or D max	5 days a week for 3weeks/ 5 weeks
Axilla	Cobalt/ 6 MV	50 Gy in 25 fractions Or 40 Gy in 15 fractions to midplane	5 days a week for 3weeks/ 5 weeks

Table 4.2.1: dose, energy and duration of different portals in breast treatment

During planning and simulation, the patients were advised radiation therapy on the basis of dose to the Organs at Risk into 15 days or 25 days. Those patients who were planned for standard fractionation or hypofractionation were included in the study after explaining the purpose of the study and getting informed consent.

4.4 DATA COLLECTION:

- This constituted the baseline data about the patient including demographics and disease characteristics of the patient were entered in the data sheet (Appendix number 3). Details regarding the initial stage, neoadjuvant chemotherapy, date of surgery, pathological staging, adjuvant chemotherapy, hormone receptor status and hormonal therapy were collected from the Medical Records in the Clinical Workstation.
- Radiotherapy details were also entered in the data sheet including the dose, fractionation, regions treated, energy, Machine, date of starting radiotherapy and date of completion of radiotherapy.
- The patients were classified into two groups either those receiving standard fractionation or those receiving hypofractionated radiotherapy over a period of 5 weeks or 3 weeks respectively. During this period the patient along with the care taker came to the hospital on all weekdays from Monday to Friday for the treatment.
- The patients received treatment either in Cobalt machine or Linear accelerator.
- Collection of Health Economics data from patients:

- Patients were explained about the purpose of the economic analysis and a informed consent was obtained. Each patient was interviewed using a pilot tested questionnaire (Appendix no 4) to collect data on the health economics initially and on a regular basis. Maximum of 30 minutes was required for data collection in each patient.

- Baseline data was collected which included demographic and social profile of the women. The demographic data regarding their hometown, occupation, marital status, parity, occupation of the children and husband. Money spent on individual's health pertaining to radiotherapy (either direct or indirect) were obtained. The patients were also asked to maintain a diary to note their daily expenses which were then reviewed

for collection of the data. They were also discussed about the mode of travel to their hometown, local travel, food and accommodation. Information was also collected about their monthly income, loss of wages due to their absence from work and loss of wages for the accompanying person. They were also asked about the source of money for the radiotherapy treatment.

The cost for the patients included

1. The direct medical cost – treatment cost, bed charges, treatment for side effects, medications and investigations charges

2. The direct non-medical cost – food, travel and accommodation for the patient and the accompanying person.

3. Cost due to productive loss – wage loss for patient and care taker

The questionnaire comprised of four parts:

1. Socio demographic profile
2. Disease characteristics - staging surgery and chemotherapy
3. Radiotherapy details
4. Costs incurred by the subjects (direct, indirect and productivity costs)

The cost effect for each were assessed at the end of the treatment.

MACHINE COSTS:

- The health care costs were derived using a format which is used for cost accounting for any procedure from the accounts department in CMC Vellore (Appendix No:5). The list of P.G. Registrars, Consultants, Physicists and Radiographers were collected and the average time spent by each of them for the various steps involved in the breast planning and treatment were calculated. The average salary for each cadre was also calculated.

- The machine details including the date and cost of purchase, annual maintenance charges for cobalt, Linear accelerator and the Simulator and other equipments in the treatment room were collected separately.

- With the help of the Accounts department staff, we calculated and derived a cost value which was the actual procedural cost. Values were separately derived for Cobalt and Linear Accelerator for duration of 15 and 25 days of breast treatment.

Assesssment of early toxicity in patients treated with standard and hypofractionated radiotherapy:

- The occurrence of early toxicity in patients treated with standard and hypo fractionated radiotherapy were recorded and analysed using RTOG acute skin toxicity criteria.

- The acute toxicities of the patient were recorded while on treatment and upto 6 weeks after the completion of the radiotherapy.

- **WEEKLY ASSESMENT:**
- The patients on hypofractionation and standard fractionation arm included in the study were monitored on a weekly basis for any side effects. Clinical examination was done for these patients to monitor any skin reactions (dermatitis) over the chest wall weekly and at the end of the end treatment. Grading of Dermatitis was done according to the Acute Radiation Morbidity Scoring Criteria.

- **POST TREATMENT FOLLOW-UP**:
- Patients were kept on follow up and were reviewed after 6 weeks of radiation therapy to assess for radiation dermatitis.

4.5 STATISTICAL ANALYSIS:

Data entry was done in Epidata and was analysed using SPSS 16.0 (Statistical Package for Social Sciences). Frequencies and percentage were calculated for discrete variables like demographic details and disease characteristics. The association between the outcome variables was tested using Independent t test. The data was represented graphically using bar diagrams and pie diagrams. Correlation between the variables was studied. The average cost of treating one patient in both arms was determined. Cost minimisation by adopting hypofractionated radiotherapy in breast cancer was determined by comparing the average costs of the two arms.

The demographic variables were analysed and mean and percentage was documented. Similar analysis was done for patient characteristics,treatment details.

Results and Discussion

5. RESULTS

- From February to August 2014, 30 patients seen in the Dept of Radiotherapy were treated with standard fractionated and hypofractionated post mastectomy radiotherapy by conventional technique meeting the eligibility criteria were enrolled in the study after an informed consent. Patients were included in either arm based on the clinical indication and choice of fractionation by the physician.

- The patients receiving standard fractionation or those receiving hypo fractionated radiotherapy received treatment over a period of 5 weeks or 3 weeks respectively. During this period the patient along with the care taker came to the hospital on all weekdays from Monday to Friday for the treatment. Patients received treatment either in Cobalt machine or Linear accelerator.

- Baseline data was collected which included demographic and social profile of the women. The demographic data included the place of origin, marital status, obstetric history, occupation of the subject, number of children, children's occupation and other dependents in the family. These variables were obtained from the subjects by a direct interview.

5.1: DEMOGRAPHY AND PATIENT CHARACTERISTICS:

Variables	Groups	Frequency	Percentage
Age	<35	4	13
	35-45	12	40
	46-55	8	27
	>55	6	20
Place	Localites (Vellore and within 100 km from Vellore)	5	16
	Other (other places of Tamil Nadu and other states)	25	84
Employmemt	House wife	26	87
	Skilled worker	1	3
	Unskilled worker	3	10
Marital status	Married	29	97
	Unmarried	1	3
Children	0	1	3
	1	11	39
	2	13	45
	3	3	10
	4	1	3
Children Occupation	Patients with children being students	11	36
	Patients with children having an employment	18	61
Other Dependents	0	24	83
	1	4	14
	4	1	3

Table 5.1.1: Demographic details

Dept of Radiotherapy caters to a wide spectrum of patients from different parts of the country; hence people of different race, ethnicity, background and lifestyle are seen. People in and around Vellore also utilize the facilities of the hospital. Hence in an economic analysis, diverse factors had to be analyzed. Affordability varies based on their socioeconomic status. Socio economic status is assessed by number of factors like education of the people, income in the family and employment. Number of dependent members in the family which includes children and other dependent members of the family like parents also indirectly attribute to this. Hence detailed data was obtained from the patients.

DISTRIBUTION OF AGE:

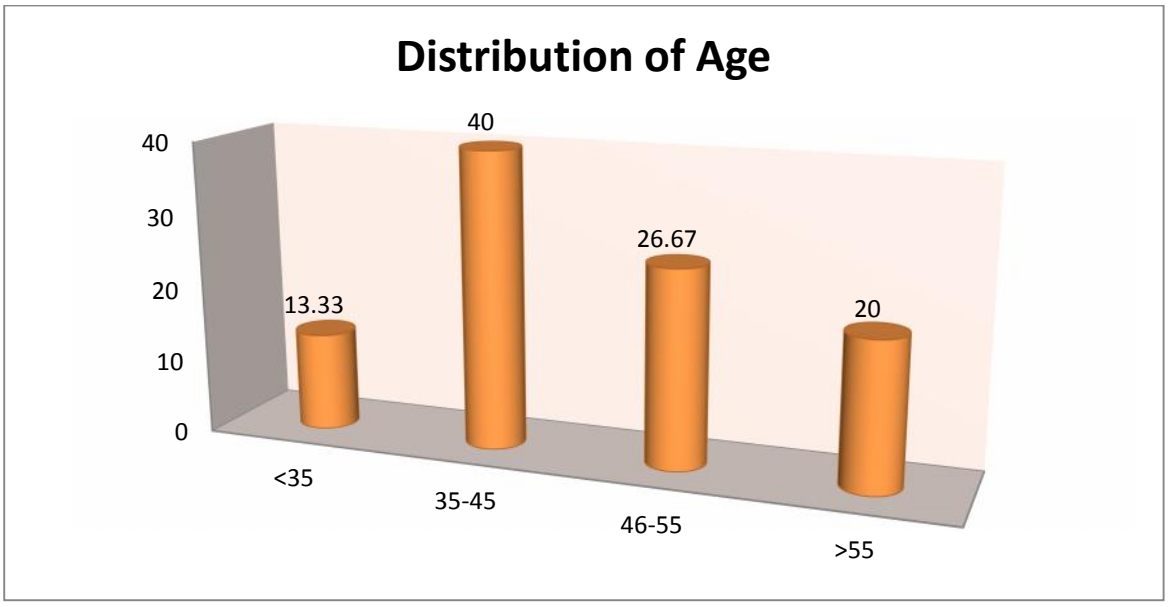


Fig: 5.1.1: Age distribution

Fig 5.1.1 shows that subjects included in the study were predominantly in the age group of 35 – 45 years, which denotes that 80% were in the earning age group.

Variable	Mean	SD	Range (Min, Max)
Age	**46**	**9.71**	**28, 67**

The mean age of the patients in the study group was 46. The age group ranged from 28 and 67. The standard deviation was 9.71.

HOMETOWN OF THE PATIENTS: LOCALITE (Vellore and within 100 km from Vellore) vs other places in TAMIL NADU and other STATES

Other Places of Tamil Nadu	Dharmapuri	1
	Namakkal	1
	Tiruchendur	1
	Thiruppur	1
Other States	Assam	3
	Andhra Pradesh	3
	Kerala	1
	Karnataka	1
	Bihar	2
	West Bengal	10
Localites	In and around Vellore	6

Table 5.1.2: Hometown of the patients

Table 5.1.2 depicts that most of our patients were from other parts of Tamil Nadu or other States. These patients had hailed from various parts of India – three were from Assam, three subjects from Andhra Pradesh, ten patients from West Bengal, two from Bihar, one patient from Karnataka and one from Kerala. Four patients from other parts of Tamil Nadu were from Tiruchendur, Nammakal, Thiruppur and Dharmapuri. Localites from in and around Vellore constituted only 20% of the local subjects (six patients).

Place	**Total treatment days**	
	n = 15 (%)	**n = 25 (%)**
Localite	**5(35)**	**1(14)**
Others	**18(65)**	**6(86)**

Table 5.1.3 : shows the treatment arm of the localites and the other states

From Table 5.1.3, we can infer that in standard fractionation arm, only one of the patient was from Vellore, rest of the six patients were from West Bengal, Kerala, Assam, Karnataka. In hypofractionated arm only five patients were from Vellore and the rest were from other places in Tamil Nadu or other States.

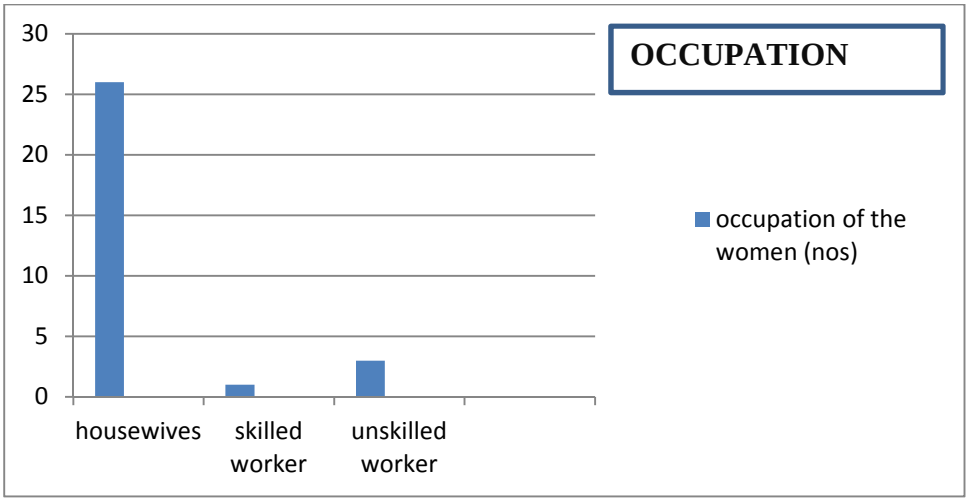


Fig5.1.2: Occupation of the patients

Fig5.1.2 gives information about the occupation of patients in the study. It is seen that most of the patients were house wives (86 %) and working group constituted a lesser percentage. They were skilled worker like teachers

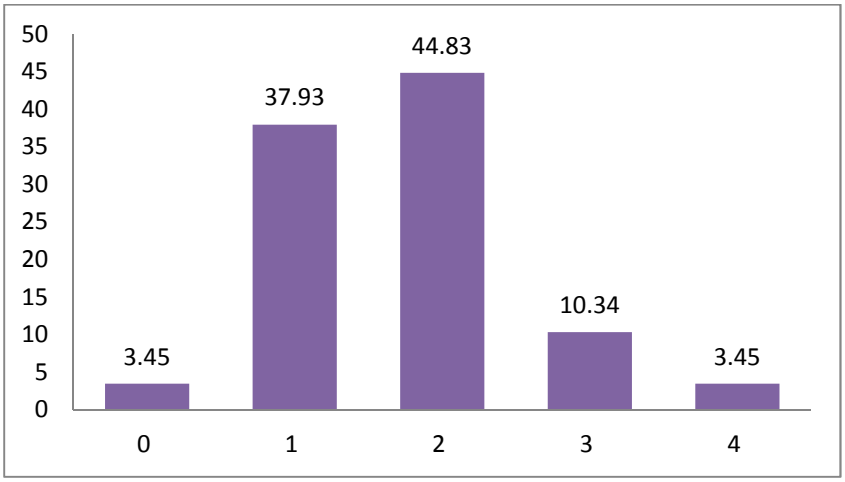


Fig 5.1.3: No of children for the patients

Out of the thirty all were married with children except for one patient who was unmarried. Fig 5.1.3 , depicts the parity of the women in the study. Forty five percent of the women had two children.

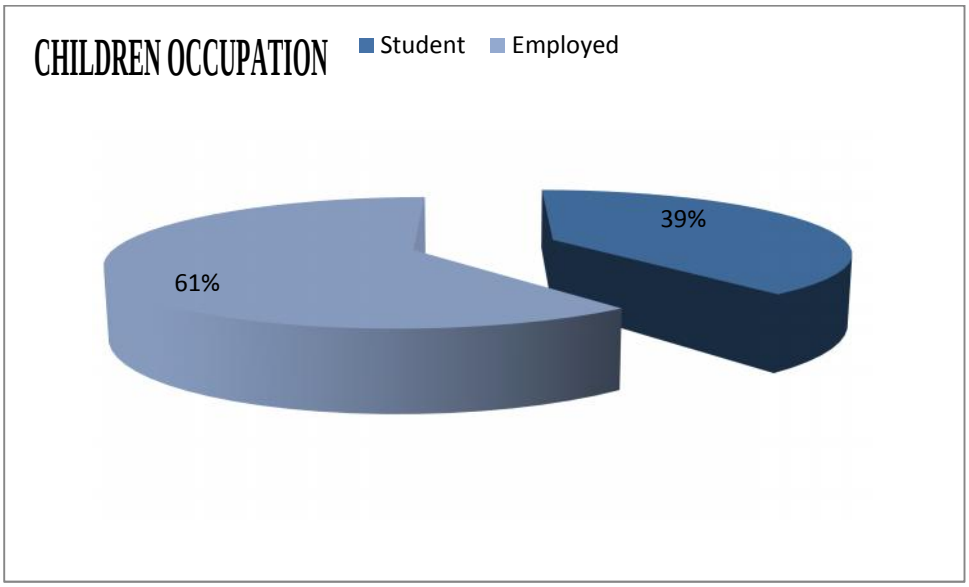


Fig 5.1.4: Children Occupation

Fig 5.1.4 depicts that 61% of the patient's children were employed and only 39 % were students

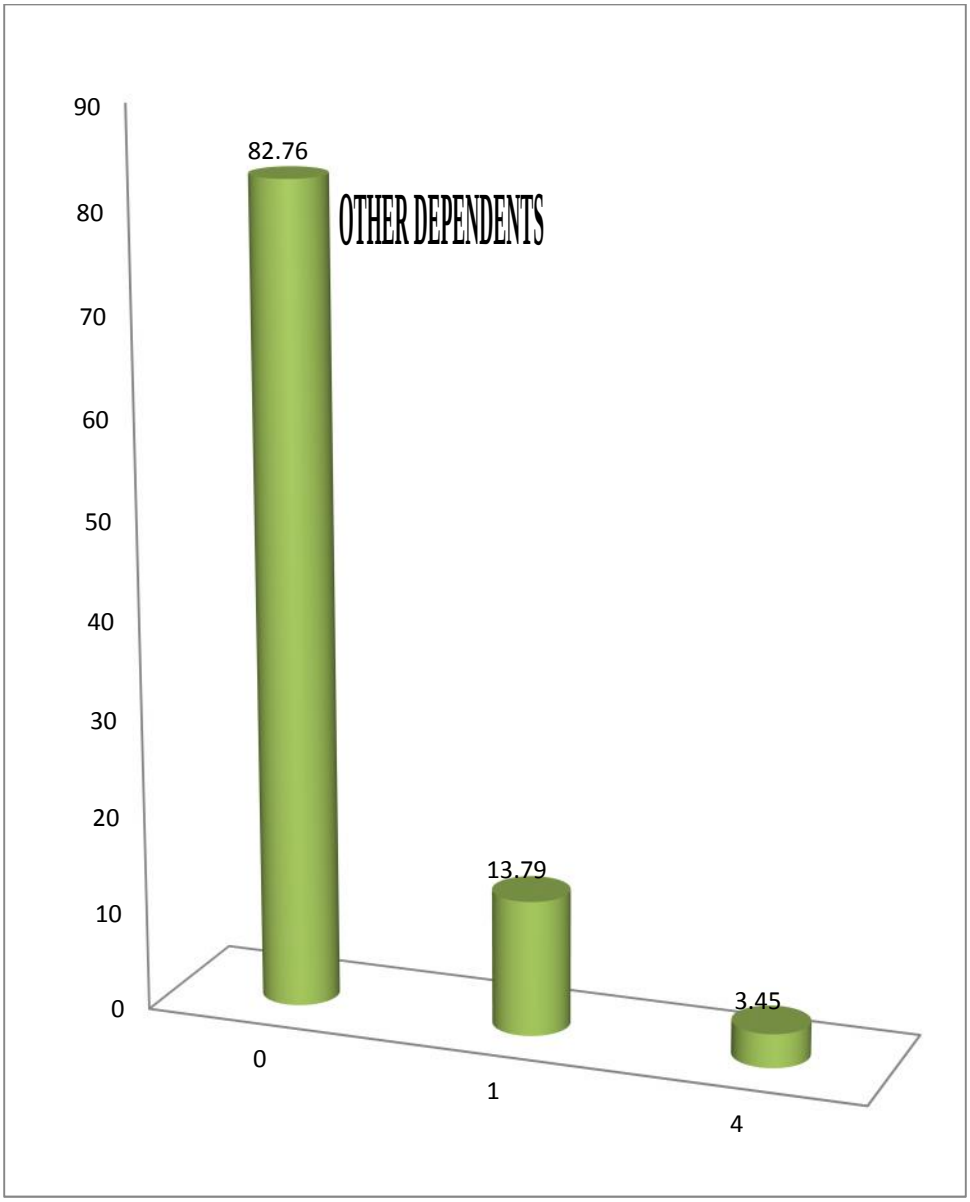


Fig 5.1.5: Other dependents in their family Fig 5.1.5, shows that more than 82 % of the patients didn't have other dependent family members in their house

COMORBIDITIES:

Variables	Groups	N	%
Comorbidities	Nil	21	70
	Present	9	30

Table 5.1.4 illustrates those patients who had other comorbidities along with breast cancer.

Three patients had diabetes Mellitus, four had Hypertension for which they oral hypoglycemic agents and anti hypertensives respectively. One had both the above and one patient had Hepatitis B for which she was on Lamivudine. The percentage of patients with comorbidities was 30%. The presence of comorbid illness and the corresponding drugs adds to the daily out of pocket expenses. The mean of the expenses for the medications was Rs. 385 in the patients with comorbidities wheras it was Rs .70 in the other persons.

5.2 DISEASE CHARACTERISTICS:

Variables	Groups	Frequency	Percentage
Laterality	Right	18	60
	Left	12	40
Regions treated with radiation	Supraclavicular region and chest wall	28	93.33
	Supraclavicular region, axilla and chest wall	2	6.67
Type of chemotherapy	Adjuvant	4	13.33
	Neoadjuvant & Adjuvant	26	86.67
ER	Positive	15	50
	Negative	15	50
PR	Positive	12	40
	Negative	18	60
Her2neu	Positive	10	33.33
	Negative	20	66.67
Molecular Subtype	Luminal A	10	33
	Luminal B	5	17
	Her 2 type	5	17
	Basal type	10	33

Table 5.2.1 :enumerates the patient characteristics with frequency and percentage

INITIAL STAGE OF THE TUMOUR:

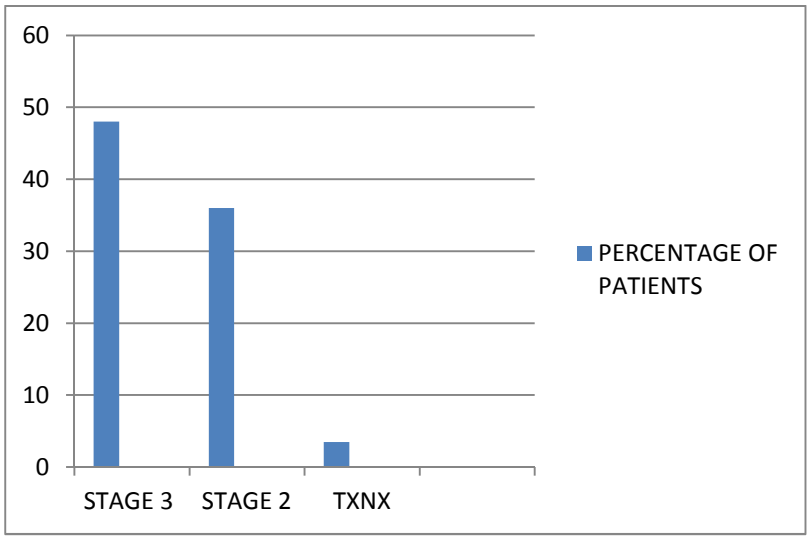


Fig 5.2.1:. depicts the stages of the patients included in the study

48% of the patients presented with stage 3 and locally advanced disease and 27% in the stage 2. Some patient who had underwent initial lumpectomy or Mastectomy with no information about the preoperative staging were classified as TxNx.(Fig 5.2.1

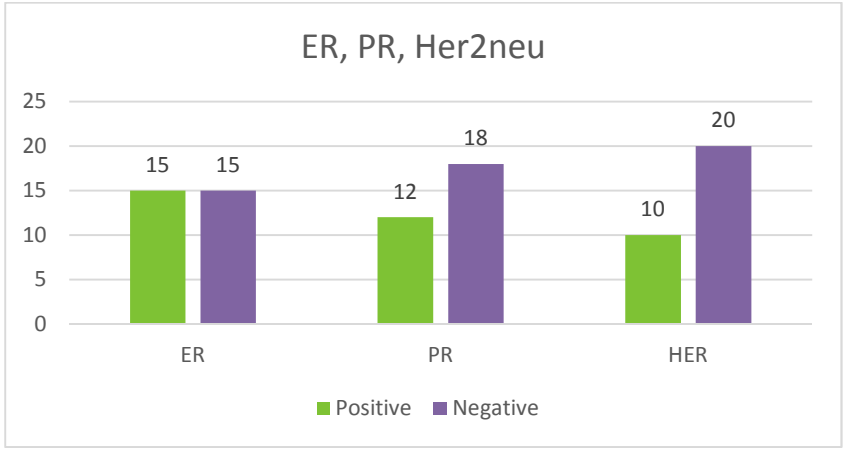


Fig 5.2.2: depicts the number of receptor positive and negative patients

Fig 5.2.2 depicts of ER, PR, Her 2 neu positivity separately. Based on the molecular classification- ten patients were Luminal A subtype, five patients were Luminal B subtype, five patients were Her 2 type and ten were triple negative or basal subtype.

Fig 5.2.3: depicts the number patients with right sided and left sided tumours

Fig 5.2.3 shows the laterality of the breast cancer. There were twelve patients with left side breast cancers and 18 patients with right sided breast cancers. These left sided breast cancer patients who have received 40 Gy in 15 fractions should be followed up for long term cardiac morbidity. Nine out of twelve left sided breast cancer patients received hypofractionation in this study.

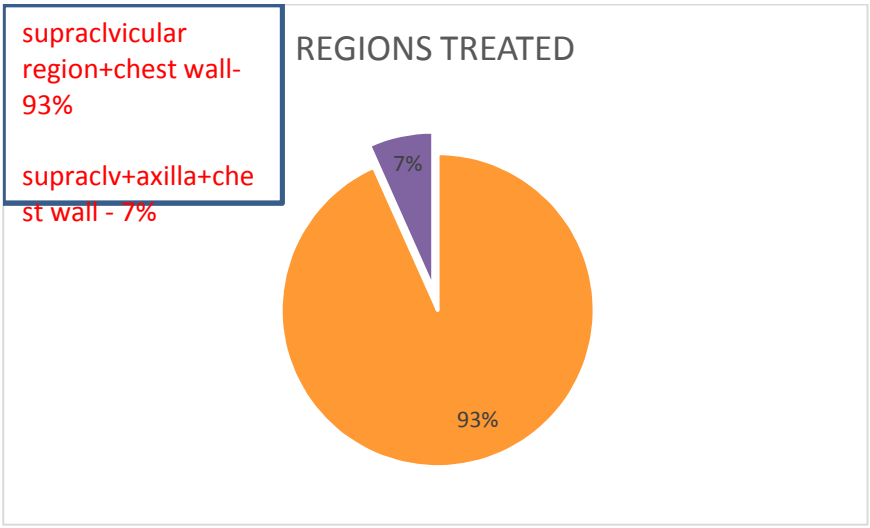


Fig 5.2.4: depicts the regions which were irradiated

Fig 5.2.4, shows most of the patients received radiation to chest wall and supraclavicular region (93%). The rest of the patients had received to the axilla as per the clinician's decision based on the clinical indication.

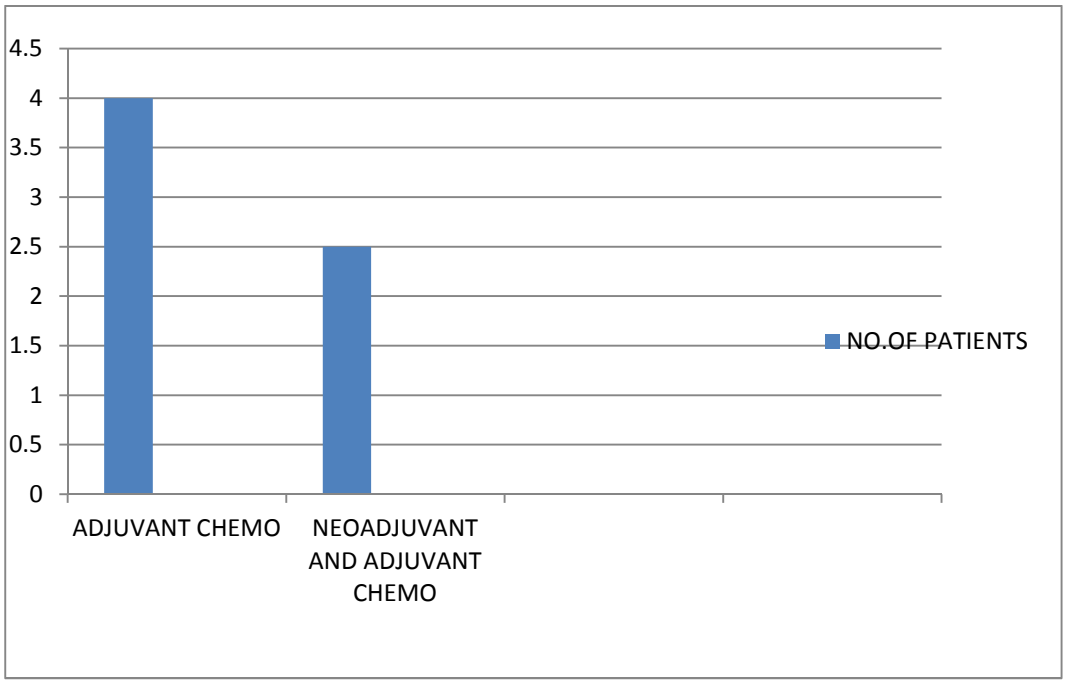


Fig 5.2.5: Chemotherapy received by the patient

Fig.5.2.5, shows the number of patients received either adjuvant or neoadjuvant chemotherapy. Twenty six patients had locally advanced carcinoma and received neoadjuvant chemotherapy followed by Mastectomy followed by adjuvant therapy. Four patients had early breast carcinoma and had upfront Mastectomy followed by adjuvant chemotherapy and radiotherapy. The neoadjuvant chemotherapy was mostly FEC/TAC based on clinical indications. The adjuvant chemotherapy chemotherapy was either Taxanes or Adriamycin based chemotherapy as clinically indicated.

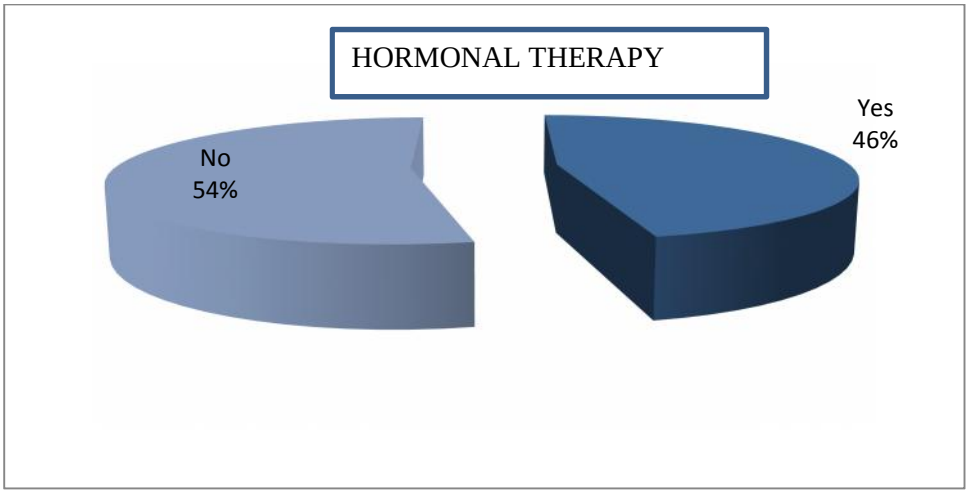


Fig.5.2.6, shows that 46 % of the patients were already on hormonal therapy, started after adjuvant chemotherapy or after surgery in all hormone receptor positive women. Hormonal therapy was either Letrazole or Tamoxifen as per the menopausal status.

5.3 TREATMENT DETAILS:
MACHINE AND NUMBER OF PATIENTS:

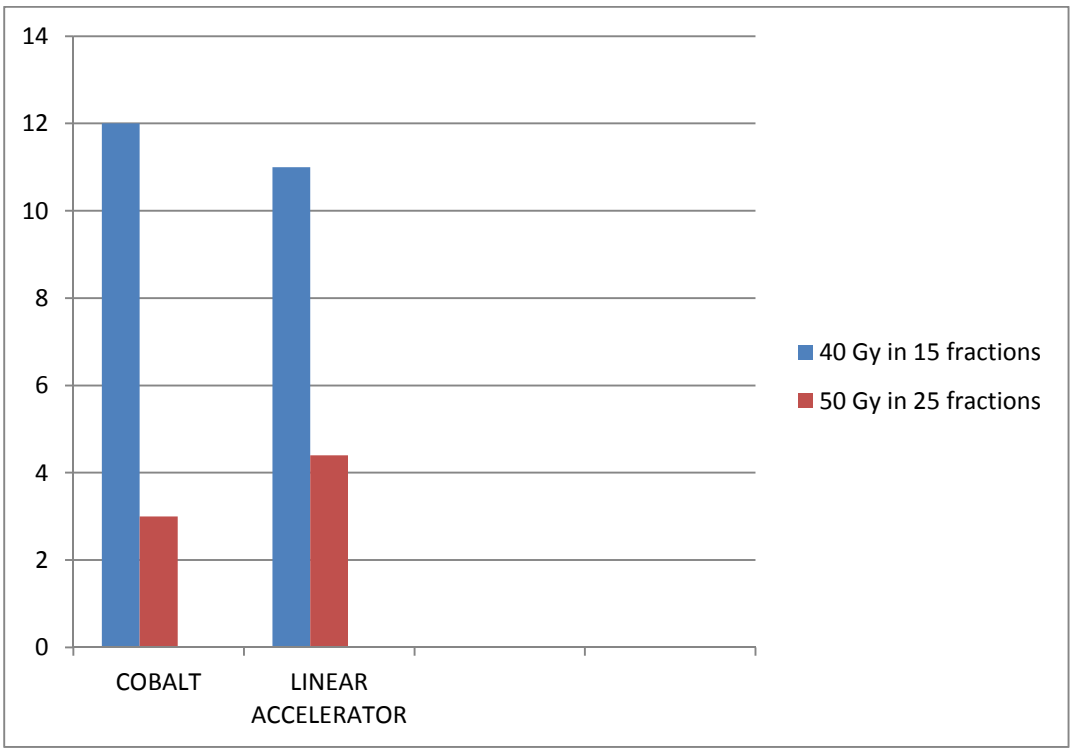


Fig.5.3.1: Figure showing the number of patients treated in Cobalt and Linear accelerator

Variables	Groups	n	%
DOSE	40Gy in 15 Fractions	23	23%
	50Gy in 25 Fractions	7	77%
MACHINE	Cobalt	15	50%
	Linear Accelerator	15	50%

Table 5.3.1: Number of patients in Cobalt and LINAC and dose fractionation

DOSE FRACTIONATION AND NUMBER OF PATIENTS:

Machine	**Number of patients in each group**	
	40Gy in 15 fractions n (%)	**50Gy in 25 fractions n (%)**
COBALT	**12(52)**	**3(43)**
PRIMUS	**11(48)**	**4(57)**

Table 5.3.1: 2 X 2 table depicting the number of patients in each arm (standard versus hypofractionation) and each machine(Cobalt and Linear Accelerator)

- Fifteen patients received radiotherapy using TeleCobalt and fifteen patients received radiotherapy in Linear accelerator.
- In Cobalt twelve out of fifteen were treated with hypofractionation and three with standard fractionation.

- In Linac eleven out of fifteen were treated with hypofractionation and four with standard fractionation.(Table 5.3.1)
- **The average time spent by the patient in the treatment room from entry to exit was noted.**

Machine	40Gy in 15 days Time per day	40Gy in 15 days Total time	50Gy in 25 days Time per day	50Gy in 25 days Total Time
Cobalt	**15 min**	**3hrs .45 min**	**10 min**	**4 hrs .10 min**
LINAC	**10 min**	**2 hrs .30 min**	**7 min**	**2 hrs .55 min**

Table 5.3.2 : shows the treatment time for the patient

- In Cobalt, we could save 25 min in which duration two extra fractions can be delivered using hypofractionation and 2 ½ fractions using standard fractionation.
- In LINAC, we could save 25 minutes during which 2 ½ fractions can be delivered using hypofractionation and 3 1/2 fractions using standard fractionation.

5.4 MACHINE COSTING :

Table 5.4.1: COSTING OF RADIOTHERAPY PLANNING AND SIMULATION

PARTICULARS	AMOUNT in Rs
PERSONNEL - Consultant, PG Registrar, RT Technician, Physicist	852.68
ELECTRICITY MAINTENANCE Medical and General Equipments	72.07
EQUIPMENT MAINTENANCE Medical Equipment, Repairs and AMC	171.47
DEPRECIATION Medical and General equipments	1193.08
INFRASTRCUTURE FACILITIES Water-1%, Building 1%, Education and Research 2% each Contingencies on expenses	87.70
INSTITUTION OVERHEAD @on expenses excludes depreciation	142.51
CONCESSION 1%	10.96

TOTAL COST PER PROCEDURE (rounded off) Rs.2510 .00

Table 5.4.2: COSTING OF RADIOTHERAPY TREATMENT DELIVERY IN COBALT 60

PARTICULARS	**AMOUNT in Rs (Per Patient/Per Fraction)**
PERSONNEL- Consultant, PG Registrar, RT Technician, Physicist	42.79
ELECTRICITY MAINTENANCE Medical and General Equipments	9.86
EQUIPMENT MAINTENANCE Medical Equipment, Repairs and AMC	17.08
DEPRECIATION Medical and General equipments	275.65
INFRASTRCUTURE FACILITIES Water-1%, Building 1% , Education and Research 2% each Contingencies on expenses	5.58
INSTITUTION OVERHEAD @on expenses excludes depreciation	9.06
CONCESSION 1%	0.70

TOTAL COST (after concession) rounded off Rs. 360.00 per patient /per fraction

FRACTION	40 Gy in 15 fractions	50 Gy in 25 fractions
	Rs 5400.00	Rs 9000.00
Weekly Check Up	Rs 101.63	Rs 169.38
Total Cost / Entire Treatment	Rs 5501.63	Rs 9169.38
ROUNDED OFF	Rs 5500.00	Rs 9200.00

Table 5.4.3: COSTING OF TREATMENT DELIVERY IN LINEAR ACCELERATOR

PARTICULARS	**AMOUNT in Rs Per day per patient**
PERSONNEL- Consultant, PG Registrar, RT Technician, Physicist	25.67
ELECTRICITY MAINTENANCE Medical and General Equipments	6.10
EQUIPMENT MAINTENANCE Medical Equipment, Repairs and AMC	231.00
DEPRECIATION Medical and General Equipments	585.80
INFRASTRCUTURE FACILITIES Water-1%, Building 1% , Education and Research 2% each Contingencies on expenses	21.02
INSTITUTION OVERHEAD @on expenses excludes depreciation	34.16
CONCESSION 1%	2.63

TOTAL COST (after concession) 900.00 per patient /per fraction

FRACTION	40 Gy in 15 fractions	50 Gy in 25 fractions
	13500.00	22500.00
Weekly Check Up	101.63 for 3 weeks	169.38 for 5 weeks
Total Cost / Entire Treatment	13601.63	22700.38

ROUNDED OFF Rs 13600.00 Rs 22700.00

Table 5.4.4: ACTUAL TREATMENT COST

MACHINE	Actual Total Treatment Costs along with Planning and Simulation	
	45 Gy in 15 fractions	50 Gy in 25 fractions
COBALT	Rs 8620	Rs.11,710
PRIMUS	Rs 16720	Rs 25820

This is the actual treatment cost which was derived by analyzing the manpower and resources in the department needed for the complete treatment of breast radiotherapy

5.5. ACUTE TOXICITIES:

SKIN REACTIONS:

Acute toxicities were assessed at the end of the treatment. Most of the patients had hyperpigmentation. Twenty three patients had grade 1 reactions and seven patients had grade 2 reactions.

Fig 5.5.1: Picture showing hyperpigmentation in a patient who had recievd 40 Gy in 15 fraction at the end of treatment

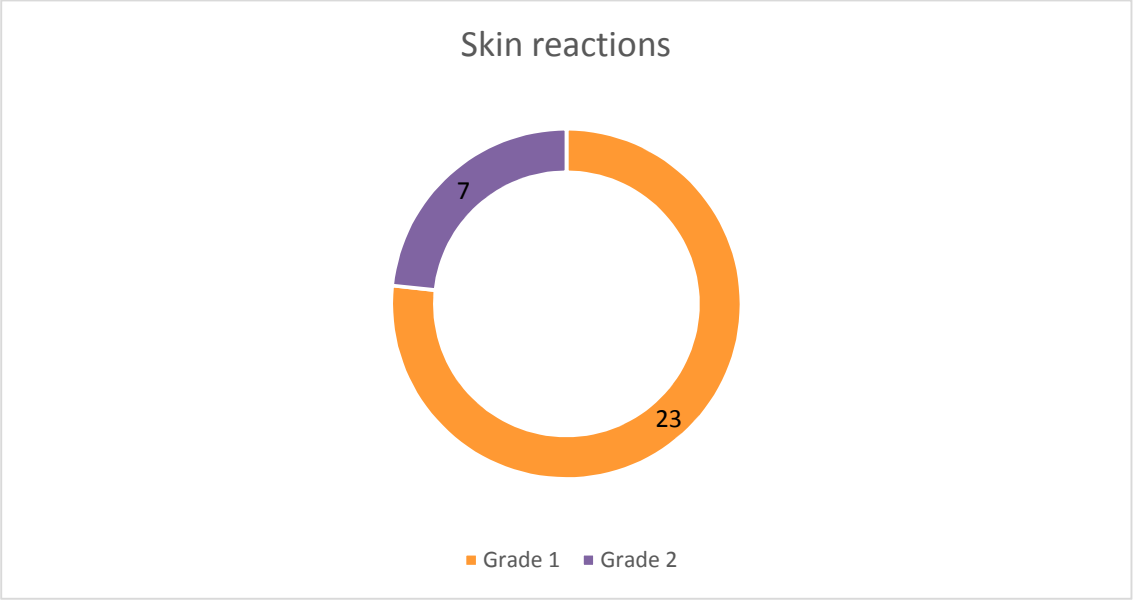


Fig 5.5.2: shows the overall incidence of grades of skin reactions

Skin reactions	Total treatment days	
	40 Gy in 15 fractions n (%)	50 Gy in 25 fractions n (%)
Grade 1	17(73.91)	6(85.71)
Grade 2	6(26.09)	1(14.29)

Table 5.5.1: incidence of skin reactions among patients treated with hypofractionation and standard fractionation.

Table 5.5.2: Table showing details and grade of skin reactions in both the arms (standard versus hypofractionation)

Other Symptoms	**Week**	**No of Patients in 40 Gy in 15 Fractions**	**No of Patients in 50 Gy in 25 Fractions**
COUGH	**Week 2 and 3**	**7 out of 23 patients**	**3 out of 7 patients**
FATIGUE	**Weed 2 and 3**	**8 out of 23 patients**	**3 out of 7 patients**

INSURANCE:

Insurance	**Yes**	**7**	**27**
	No	**19**	**73**

Seven out of thirty patients had treatment under the cover of insurance. Investigations were not included in the insurance. Those patients who had insurance cover were from Vellore or

from Tamil Nadu. The out of pocket costs were still there for these patients which was spent for patient and the relative's food and accommodation, travel from their home and daily travel to the hospital. They also spent specific amount ranging from Rs.200 to Rs.500 for applying and sanction of the insurance.

Three patients received concession for the investigations and treatment (in view of the poor socio-economic status and affordability). The expenditure incurred by the patients was

5.6 PATIENT COSTING AND EOCNOMIC ANALYSIS:

STATISTICS FOR THE COSTS -- 15 DAYS VS 25 DAYS INTERPRETATION:

Direct medical costs:

Direct medical costs were calculated including the investigations, medicines and the actual treatment cost. The mean is Rs. 13587, 95% C.I (11661 to 15513) for 15 days compared to Rs. 213386, 95% C.I (14450 to 28272) for 25 days treatment. Table 5.6**.1** shows the mean and 95% C.I for each cost separately for 15 days vs 25 days.

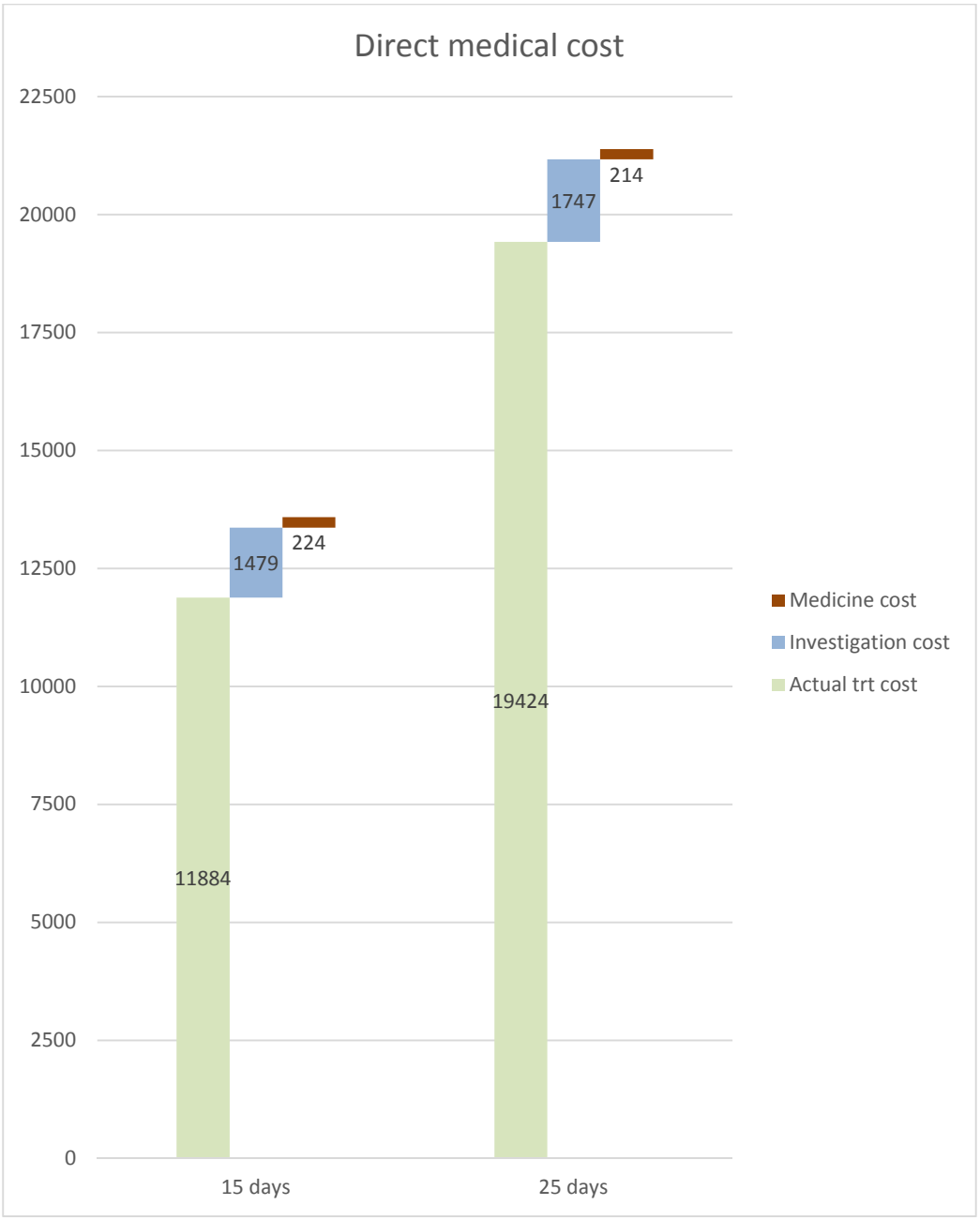


Fig 5.6.1: Stacked bar diagram for the direct medical costs for treatment in 15 days vs 25 days

TYPE OF COST	STATISTICS	COST FOR 15 DAYS IN INR	COST FOR 25 DAYS IN INR
Actual Cost	**Mean (95% CI)**	**11884 (10095 to 13673)**	**19424 (12750 to26098)**
Investigation Cost	**Mean (95% CI)**	**1479 (1165 to 1794)**	**1747 (-38 to 3533)**
Medicine Cost	**Mean (95% CI)**	**224 (113 to 335)**	**214 (42 to 387)**
Direct Medical Cost	**Mean (95% CI)**	**13587 (11661 to 15513)**	**21386 (14450 to 28272)**

Table 5.6.1 shows the mean and 95% C.I for each cost separately for 15 days vs 25 days.

Direct non medical costs:

Table 5.6.2, shows the mean and the 95% C.I for each cost separately for 15 days vs 25 days.

Indirect medical costs were calculated including the patient and the relative's food, accommodation daily local travel expenses, travel expense from their hometown and care giver's expenses. Mean and the 95% C.I was calculated each of the nonmedical costs. The mean of direct nonmedical costs were significantly lower for the 15 days arm compared to the 25 days arm. Figure 5.6.2 and 5.6.3 illustrates the the non medical costs for the patient and the relatives respectively.

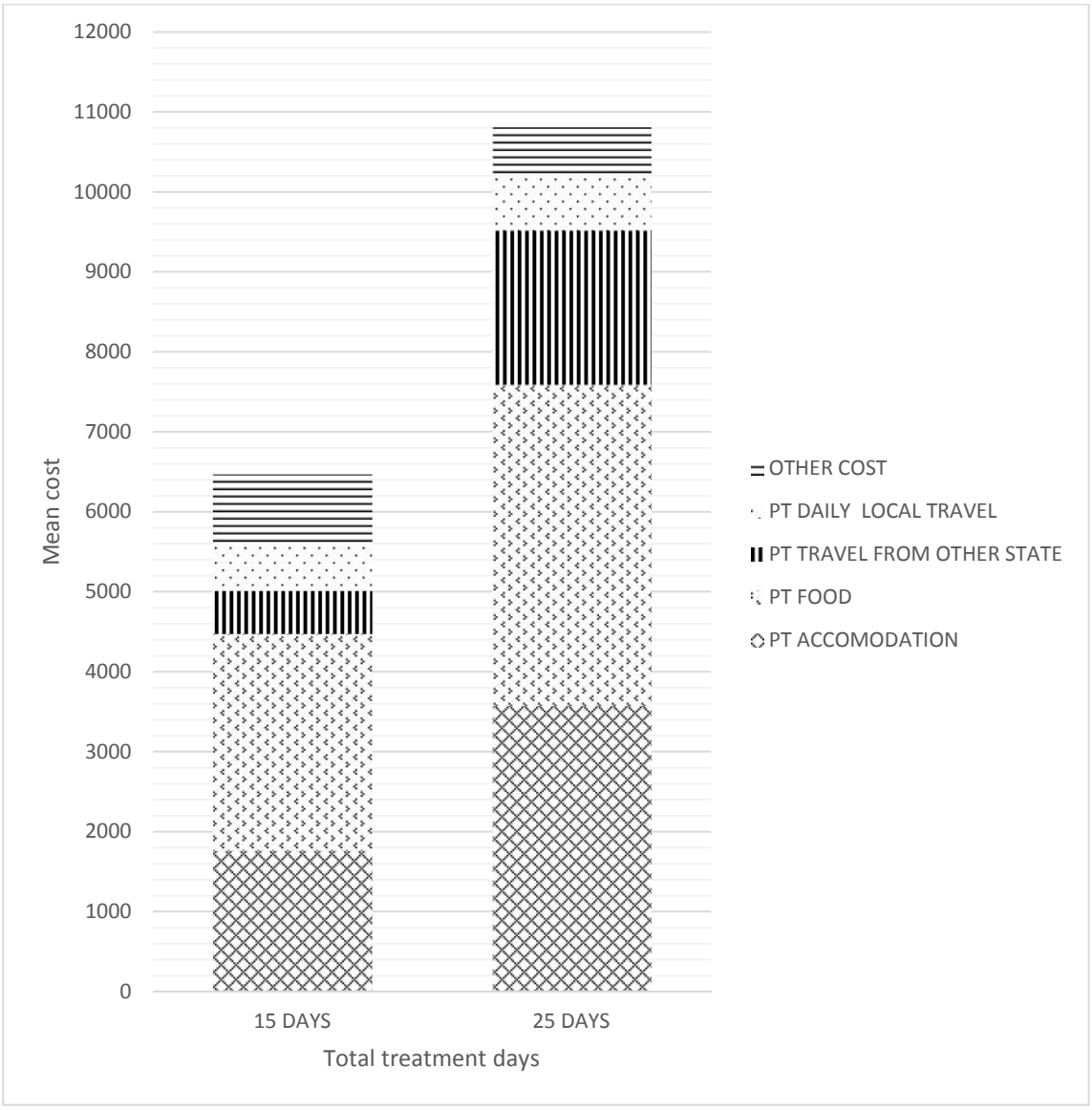


Fig 5.6.2: Stacked graph showing the patients' non medical costs in both the arms

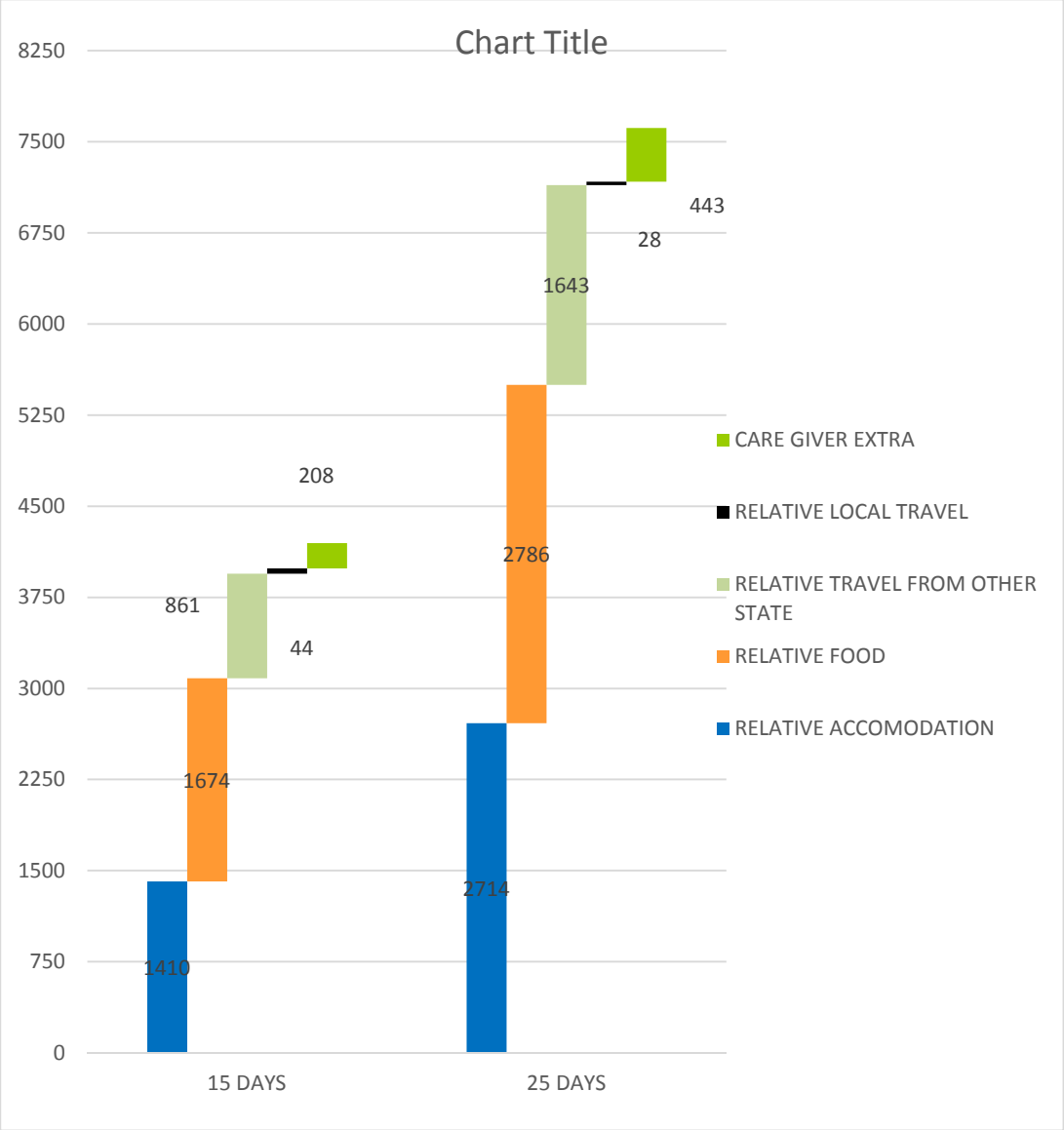


Fig 5.6.3: Stacked graph illustrating the expenditure for the relatives (non medical costs)

NON MEDICAL COSTS:

COST	STATISTICS	15 DAYS	25 DAYS
PATIENT ACCOMODATION	MEAN (95% CI)	1758 1258 to 2260	3571 1657 to 5486
PATIENT FOOD	MEAN (95% CI)	2713 2050 to 3376	4000 2489 to 5510
PATIENT TRAVEL FROM OTHER STATES	MEAN (95% CI)	542 223 to 860	1928 109 to 3748
PATIENT DAILY LOCAL TRAVEL	MEAN (95% CI)	593 198 to 990	696 71 to 1322
OTHER COST	MEAN (95% CI)	865 398 to 1333	614 261 to 867
RELATIVE ACCOMODATION	MEAN (95% CI)	1410 994 to 1827	2714 1555 to 3873
RELATIVE FOOD	MEAN (95% CI)	1674 1307 to 2040	2786 1866 to 3705
RELATIVE TRAVEL FROM OTHER STATE	MEAN (95% CI)	861 493 to 1229	1643 -220 to 3506
RELATIVE LOCAL TRAVEL	MEAN (95% CI)	44 12 to 77	28 3 to 53
CARE GIVER EXTRA	MEAN (95% CI)	208 96 to 321	443 37 to 849
DIRECT NON MEDICAL COSTS	MEAN (95% CI)	10671 8699 to 12642	18424 10711 to 26137

Table 5.6.2: Table gives information of all the direct non medical costs separately for 15 dats versus 25 days

PRODUCTIVITY LOSS:

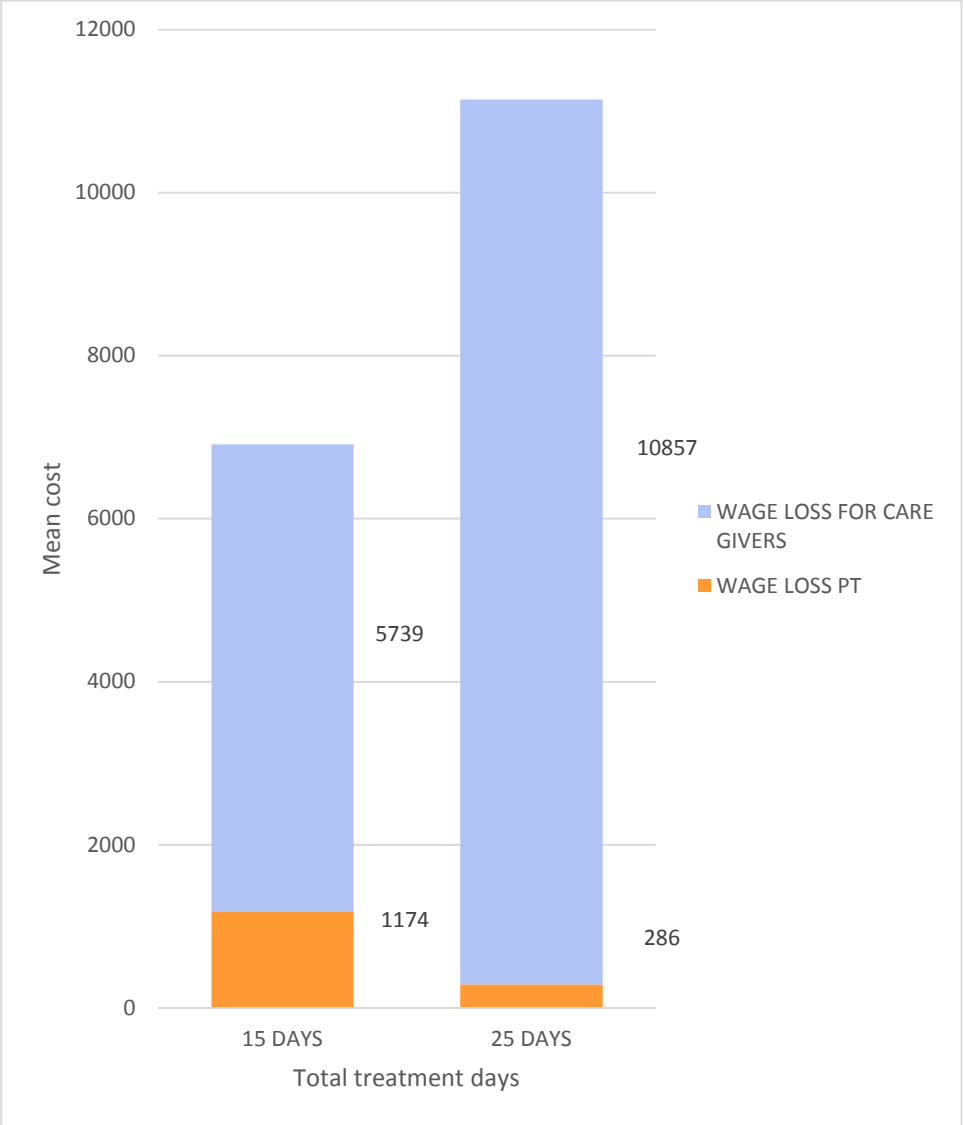


Fig 5.6.4: Figure showing the productivity loss for the patient and the care giver for 15 days versus 25 days

COST	STATISTICS	15 DAYS	25 DAYS
Wages Lost Patient	**Mean (95% CI)**	**1174 -11 to 2360**	**286 -413 to 985**
Wages Lost Care Giver	**Mean (95% CI)**	**5739 4571 to 6907**	**10857 7679 to 14035**
Productivity Loss	**Mean (95% CI)**	**6913 5164 to 8662**	**11143 8346 to 13939**

Table 5.6.3 gives the productivity loss for the patient and the care giver for 15 days versus 25 days

Table 5.6.3 shows the productivity loss, which was calculated summing the loss of wages for the patient and the relative. The mean was Rs.6913, 95% C.I (5164-8662) for 15 days compared to Rs.11143. 95% C.I (8346 – 13939) for 25 days treatment. The mean of the productivity loss was lower for the 15 days arm than the 25 days.

ANALYSIS:

Independent t- test was done for the analysis.

Table 5.6.4: COSTS FOR COBALT VS PRIMUS

COSTS	MACHINE	STD.ERROR	DIFFERENCE IN MEANS	t- TEST p- VALUE
Direct Medical Costs	COBALT PRIMUS	475 1137	-10171	0.006
Direct Non Medical Costs	COBALT PRIMUS	1730 1644	352	0.082
Productivity Loss	COBALT PRIMUS	696 1365	-1533	0.326
TOTAL COST	COBALT PRIMUS	2662 3275	-11353	0.012

T- test was done for the direct medical, direct nonmedical costs, productivity loss separately for the Cobalt and the Primus (Linear Accelerator). The p value was significant for the direct medical and nonmedical costs except for the productivity loss. (Table 5.6.4)

Table 5.6.5:ANALYSIS FOR COBALT FOR 15 DAYS VERSUS 25 DAYS

COSTS FOR COBALT	DAYS	MEAN	STD.ERROR OF MEAN	DIFFERENCE IN MEANS	t- TEST p- VALUE
Direct Medical Costs	15 25	9471 13718	157.8 393.2	-4246	0.003
Direct Non Medical Costs	15 25	10750 20280	1558.1 3875.5	-9529	0.021
Productivity Loss	15 25	6250 10666	616.9 881.9	-4416	0.005
TOTAL COST	15 25	26471 44665	2064.8 4674.4	-18193	0.002

T test was done for Cobalt for 15 versus 25 days. The p value was significant favouring 15 days for the direct medical costs, nonmedical costs and productivity loss. The p value for the direct medical costs was 0.003 that of the non medical costs is 0.021, productivity loss is 0.005 and p value for the total costs is 0.002, which is statistically significant **(**Table 5.6.5).

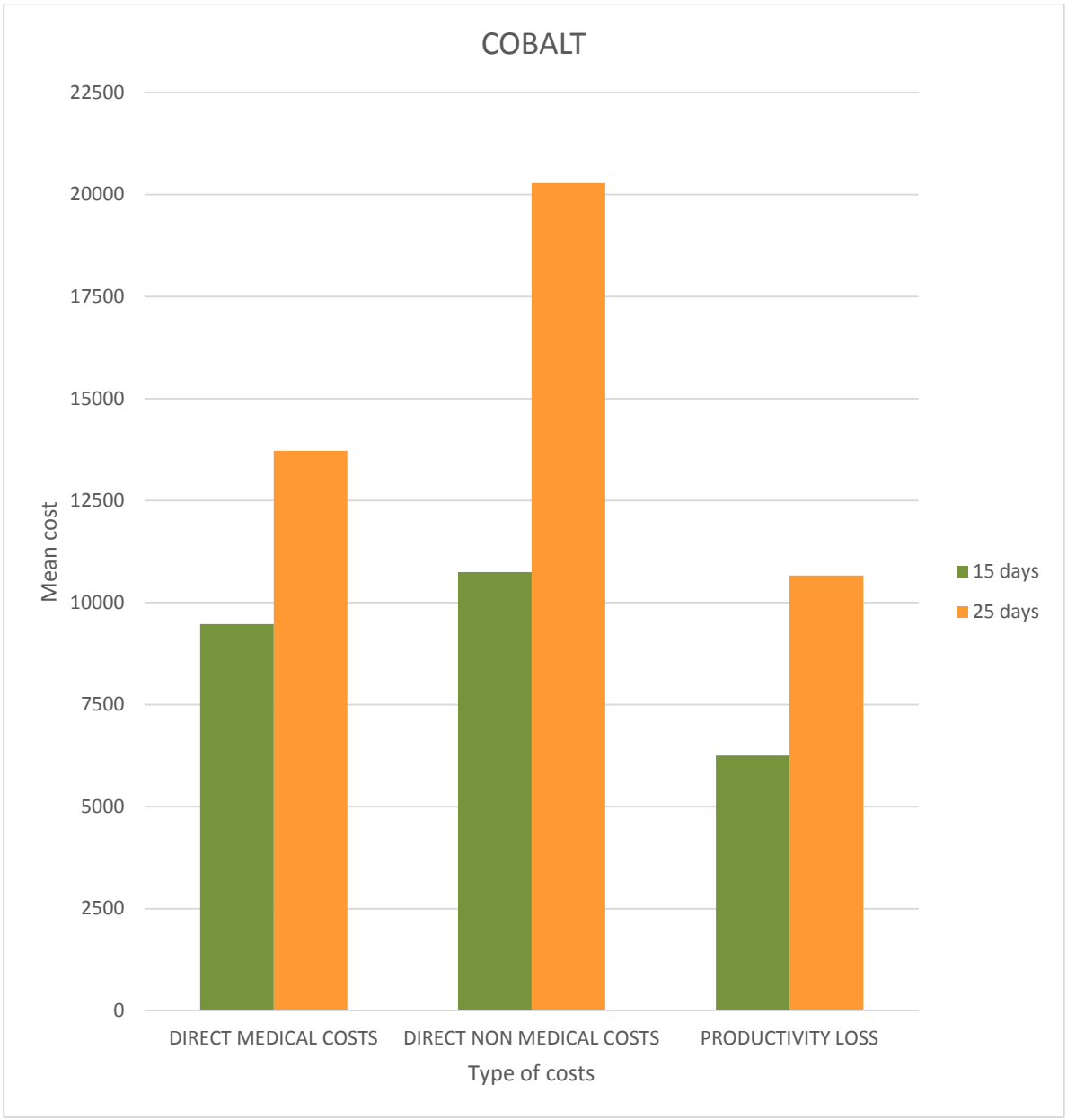


Fig 5.6.5: Bar diagram showing the types of cost and their mean cost for cobalt for 15 days versus 25 days

Table 5.6.6: ANALYSIS FOR LINAC FOR 15 DAYS VERSUS 25 DAYS

COSTS FOR LINAC	DAYS	MEAN	STD.ERROR OF MEAN	DIFFERENCE IN MEANS	T- TEST p- VALUE
Direct Medical Costs	15 25	18077 27136	269.8 1385.6	- 9059	0.006
Direct Non Medical Costs	15 25	10584.5 17032.5	1114.2 5075.2	-6447	0.082
Productivity Loss	15 25	7636 11500	1647.4 2020.7	-3863	0.180
TOTAL COST	15 25	36298 55669	1845.2 8047.8	-19370	0.004

T test was done for LINAC for 15 vs 25 days. The p value did not show significance for nonmedical costs and productivity loss. The p value for the direct medical costs was 0.006 that of the non medical costs is 0.082, productivity loss is 0.180 and p value for the total costs is 0.004 (Table 5.6.6)

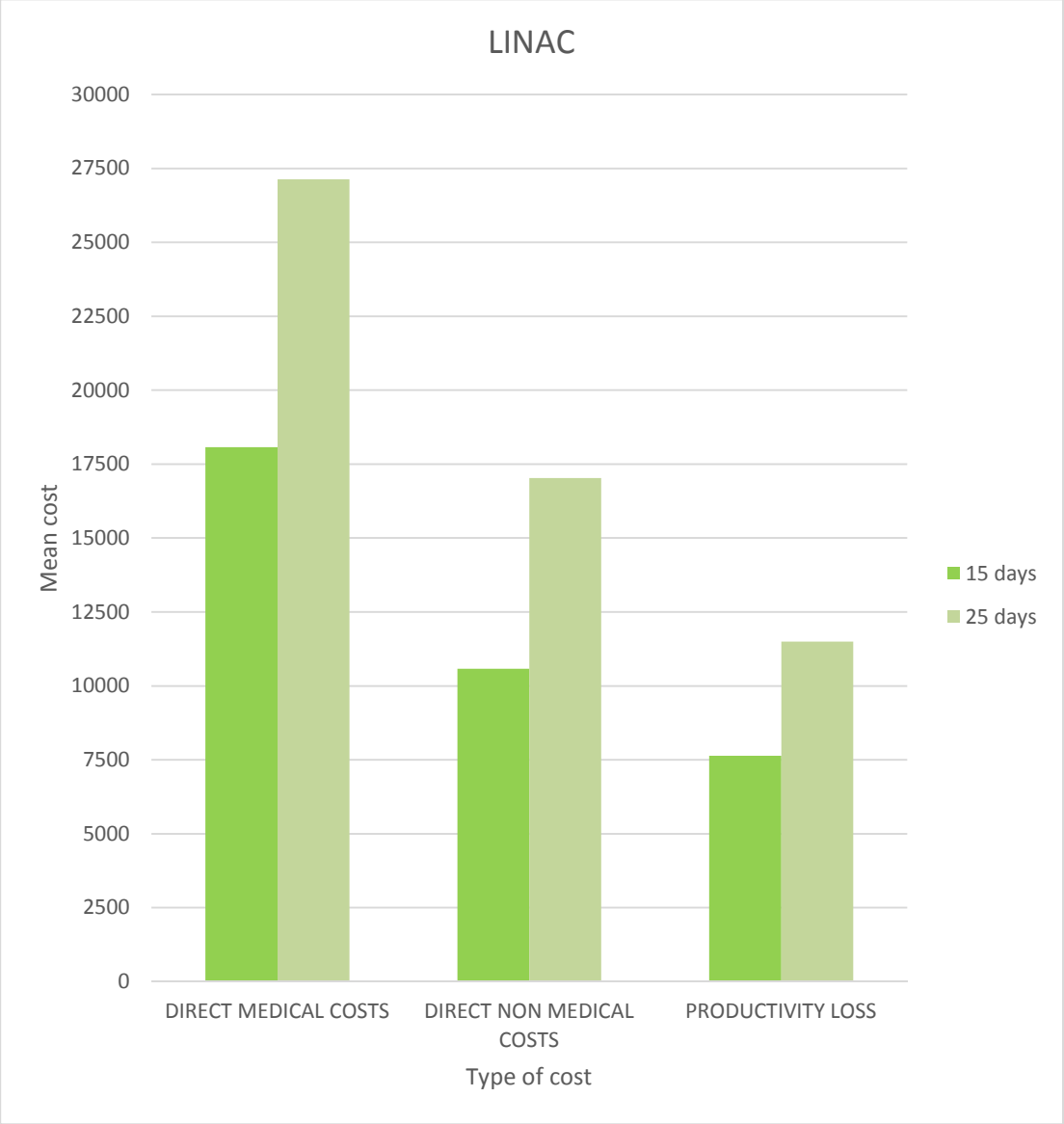


Fig 5.6.6: Bar diagram showing the types of cost and their mean cost for LINAC for 15 days versus 25 days

6. DISCUSSION:

Financial hardships in families of cancer patients:

Nearly one-half of patients are reporting to private health facilities as the first point of contact for cancer related diseases. More than three-fourths of the cancer patients faced financial constraints in management. Due to financial problem, poor families delay their treatment decision. (51)

The SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment) was done to improve outcomes for seriously ill hospitalized adults by improving information and decision-making. They enrolled 2652 patients in the intervention arm and 2152 in the control arm of a block-randomized trial of enhanced information, counseling, and support. They had analysed that around one third of the families had lost most of their savings following treatment for cancer and in one fifth of the family, a member quit work or had changed their lifestyle to provide care for the patients. Because of limited resources, poor families had financial hardships.(52)

The poor become poorer due to the expensive cost of diagnosis and treatment. Modern technology though proved to be effective in curing the diseases the costs of diagnosis and treatment, have consequently increased due to the technology costs.

Increase in out of pocket costs: (56)

With regard to high out-of-pocket payments, it is essential to reduce the financial burden to the poor patients, thereby enabling them to access treatment services. Patient has to pay for transportation and child-care especially in Indian scenario where patient has to travel farther to the tertiary care facilities. While hospitalization do requires an accompanying person, most of the time they are adults and that person’s time is a direct cost. Friends and family also provide informal assistance to the care of patient. Patients requiring multimodal

form of treatment including surgery and chemotherapy incur a higher expenditure. Most often, depending on their type and stage of cancer, patients would require more than one form of treatment. All the three modalities of treatment are highly expensive and when it is combined modality of treatment, patients are financially knocked down. Moreover, the duration of the entire treatment taking more than six months and throughout the period of treatment they are dependent on others for finances or self care. Hence apart from the direct medical causes by the treatment, nonmedical causes also shoot up. This pushes the families to deep financial crisis when cancer treatment is expensive and is also long term with no surety of cure.

Minimising the duration of radiotherapy

Radiation therapy as an integral part in the multi-modality management of breast cancer significantly reduces the loco regional recurrence and also improves the overall survival. The conventional way of radiotherapy in breast cancer imparts larger expenses to the patients. To overcome this economic burden and to minimise the acute toxicities of conventional Radiotherapy, various Hypo fractionated schedules were tried and had proven beneficial in terms of local control and overall survival.

But there is more to it for society than just costs. In the context of societal objective of deriving the maximum health benefits from invested money, it is inevitably essential to identify which health outcomes can be expected from a given treatment. The optimal allocation of resources is better facilitated when the information on both the efficacy of medical interventions and their costs must be balanced against each other in a systematic fashion. To do so, economic evaluations (e.g. cost-effectiveness) and cost-utility analyses are being done.

The shorter fractionation schedules are equally efficacious and tolerable for the Indian women. The out-of –pocket costs incurred during radiotherapy is reduced by minimizing the treatment duration. The reduction in duration helps in better utilization of available resources. The landmark trials are the UK standardization of breast radiotherapy (START) Trials which have laid evidence for hypofractionated radiotherapy for patients with breast cancer. START B trial had compared conventional standard schedule with hypofractionated regimen. (40 Gy in 15 fractions).Most of the patients in the trial had breast conservation surgery and only 8% of the patients had undergone Mastectomy.

The economic impact of hypofractionated schedules can be evaluated by weighing the costs to effectiveness(42). This was analysed in a Markov model- that is cost effectiveness data was modeled with factors like impact of recurrence, cosmetic outcome and late side effects by Hayman et al(53). Many of the radiotherapy centers in UK and Canada have already adopted hypofractionated regimens routinely (42).

But late cardiac toxicity makes other nation to hesitate to adopt the same. But recently study of 7000 Canadian women, where the impact of cardiac mortality was analysed shows deviation of curves for cardiac death(54). After the START trial there has been acceptance of the hypofractionated approach and many leading radiotherapy centres in India have adopted the same. In this study the cost minimization that may be experienced by introducing a hypofractionated approach in breast cancer radiotherapy has been studied

This was a single arm prospective study design to assess the cost minimization between standard and hypofractionated arm.

Demographics :- how do they influence the costs?

The demographic data included the place of origin, marital status, obstetric history, occupation of the subject, number of children, children's occupation and other dependents in the family . The mean age was 46 in this study which is similar to the data from most of the similar studies in India, herein the mean age at presentation was 47(55)

Occupation of the patients:

In this study, around 90% were housewives. A similar study by MAMSI (Moulana Azad Medical college, New Delhi) depicted their study population had > 94% as housewives in the breast cancer group. (55) Housewives do contribute to immense hardwork in their houses which indirectly contribute to their income of their spouses. The work done by housewives is often not accounted to the loss of wages or productivity losses. The patients who are basically housewives, when they are away from their home for treatment, they require extra hands/ care givers help to look after their children and their work to compensate for their absence.

Hence, the fact is that housewives indirectly require help from other people , thus increasing their total expenses . This is included in the questionnaire, as " care givers" who are required , to look after the children and house hold work in the absence of these patients at their home.

The term caregiver means as defined in public health as a family member, friend, or neighbor who takes care of a person who has chronic ailments and needs help to manage a variety of tasks. Some people also required an extra person apart from the relative accompanying for the treatment, to assist them for their daily activities. These person had to travel daily or come whenever necessary. Hence as the duration of stay increases the

expense for the care giver also increases. The mean expense for the care giver was Rs 208 versus Rs 445 in the two arms, 40 Gy and 50 Gy respectively.

Children's occupation:

17 out of 30 patients had their children who were employed and because of that fact their children were able to support their family financially. It was also seen that eight of the patients were accompanied by their children who were employed. So there is also a problem of loss of productivity for these patients when the working groups of children accompany them for treatment taking leave from their concerned working places.

Other dependents:

The data on dependent members of the family and the number of children indirectly gives information about the scattering of finances of the monthly income which might be indirectly affected due the present expenses for treatment of breast radiotherapy. Other dependents , as informed by the patients were either their parents or their in laws who were staying with the patients' family in their hometown.

Co morbid illness:

The presence of comorbid illness and the corresponding drugs adds to the daily out of pocket expenses. The mean of the expenses for the medications was Rs. 385 in the patients with comorbidities wheras it was Rs.70 in the other persons.

Local lodgings:

The hometown of the patients is of importance in this economic assessment studies, because the travel and the stay expenses made by the patients who are from other places and other states contributes a sum of amount which are the significant out of pocket expenses and predominantly contributes to the non medical costs of the patient. They are bound to stay outside the hospital either in lodges or house for rent for the entire treatment of breast radiotherapy for the known fact that radiotherapy is offered over a period of 3- 5 weeks on

daily fractionated basis. People who came to our hospital predominantly stayed in nearby lodges whose daily rent varied from Rs 60 per day to Rs 500 per day. Some people had rented a house in the adjacent areas whose monthly rent ranged from Rs 3000 per month to 7500 per month. 94% of the patients had stayed in lodges whose rent is calculated on daily basis. Hence decreasing the treatment duration from 5 weeks to 3 weeks will bring down the total accommodation costs of the patient. The mean of the accommodation costs for the patient and the relative was Rs.3510 and Rs.6285 in the 40 Gy arm and 50 Gy arm respectively.

Transport:

The lodges and the houses were located either near to the hospital or at a distance of 3- 5 kms from the hospital. The patients who stayed and houses at 3- 5 kms had to use local transport facilities for reaching the hospital daily. The localite patients, who were residing in and around Vellore, also used local transport facilities daily to reach the hospital. All of our patients had received Radiotherapy on OPD basis and none of them were admitted in bed for the same or for any complications.

Source of income for radiotherapy treatment:

The patients had to borrow, sell their assets or utilize from their saving for the radiotherapy treatment. Among our patients sixteen out of thirty had borrowed from known person, seven patients had utilized the Chief Ministers health Insurance (patients from Tamil Nadu), four had sold their assets (land) and three had utilized their savings.

Direct medical and non medical costs:

The direct medical costs (mean) was Rs. 13587 and Rs. 21386 for 15 days and 25 days respectively irrespective of the machine used for treatment. This accounts for 56% and 53% of the total expenses for the two arms respectively.

The direct non medical costs (mean) was Rs. 10671 and Rs. 18424 for 15 days and 25 days respectively irrespective of the machine used for treatment. This accounts for 44% and 47% of the total expenses for the two arms respectively.

In a study done **in All India Instititute of Medical Sciences (44**) to compute the cost during the course of radiotherapy, it was found that 59% of the patients' expenses were spent for food, lodging and transportation, whereas 41 % was only utilized for the direct medical costs.

Cost computation Cobalt and Linac:

Comparing the cost of treatment in Cobalt machine between the hypofractionated and the conventionally fractionated arm there was significant difference in the direct medical costs with a mean of Rs.9471 versus Rs.13718 respectively (p= 0.003).

The non medical costs was also associated with significant difference with mean of Rs.10750 versus Rs.20280 for 40 and 50 Gy (p=0.021).The loss of productivity was also significant favoring hypofractionated arm with the mean costs of Rs. 6250 and Rs.10666 (p= 0.005) in the two arms.

On the whole, the total costs were lower with 40 in 15 fractions arms compared to 50 Gy in 25 fractions (p value =0.002) which is statistically significant.

In Linear accelerator, the costs were analyzed and compared. Direct costs and the non medical costs were significant was (p=0.006 and 0.082 respectively). The productivity loss didn't show any significance with the mean loss of Rs 7636 versus Rs.11000 (p value of 0.180). But the total costs were lesser in the 40 Gy arm implying its significance.

The difference in the productivity loss was more in the 15 days arm because the average income of the patient who was working was more in this arm compared to 25 days arm. This can also be attributed to the reason that mixture of patients of different socio economic status were in the study group which may be the confounding factors for this difference.

This can be explained by the fact that all the localites and the patients from other states were analyzed together. There was also difference in the amount spent for the accommodation based on the affordability even among the same arm of 15 days, ranging from 60 Rs per day to Rs 400 per day. Hence the mean value of 15 days versus 25 days becomes different to correlate as more patients who received radiotherapy for 15 days stayed in costlier lodges and so the lodging cost were significantly low for 25 days group.

Hospital perspective:

Medical and personnel resources were also analysed which showed significant reduction in resource utilization and time consumption in the 15 days group. In Cobalt, the average treatment time was 3 hour and 45 minutes versus 4 hours and 10 minutes in 40 and 50 Gy respectively for the entire duration of treatment. So we could save 25 min in which duration two extra fractions can be delivered using hypofractionation and 2 ½ fractions using standard fractionation.

In LINAC, the average treatment time was 2 and half hours versus 2 hours and 55 min for the entire treatment in 40 and 50 Gy respectively. Here also we could save 25 minutes during which 2 ½ fractions can be delivered using hypofractionation and 3 1/2 fractions using standard fractionation. This may be advantageous for the radiotherapy departments since it may reduce the patients waiting time especially in hospitals which have large waiting list.

Acute toxicity:

Only two patients had received radiation to axilla also based on the clinical and pathological indications. When axilla was also included, intense skin reactions may be anticipated, especially in obese patients due to the axillary folds. Those patients who had received radiation to axilla were treated with 50 Gy.

The patients tolerated the treatment with 7 patients developing not more than Grade 2 reactions. 23 manifested with Grade 1 reactions. All patients had hyperpigmentation which was slightly more in patients treated with Cobalt. Grade 2 reactions were manifested in 6 out of 7 patients treated with 40 Gy in 15 fractions with only 1 patient in 50 in 25 fractions arm. But none of the patients developed severe reactions like ulceration. Overall 40 Gy in 15 fractions was tolerated well with respect to the skin reactions.

6.1 LIMITATIONS:

- This study is a single institutional study which includes diverse demographic details and subjects of spectrum of socioeconomic status.
- Patients treated with Cobalt and Linear accelerator were analysed together.
- Patients hailing from in and around Vellore and those from other parts of Tamil Nadu and other States were not separately analysed.
- Long term analysis of locoregional control and overall survival is needed to follow up the costs which may occur in case of recurrence/ late complications.
- General attitude of an individual in India is not to reveal the cost correctly, and some of them did not report clearly, thus, cost estimation may not be accurate.

- Hence, precise estimation of non medical cost and loss of productivity of patient and relative could not be determined, thus, study of cost estimates do not cover costs of many individuals correctly.

In order to formally validate this therapeutic approach from a societal perspective, cost effectiveness evaluations weighing long-term outcome against the societal costs incurred until many years after treatment are needed.

7. CONCLUSION

To conclude, our study estimates the direct and indirect medical costs for a range of cancer subjects on the basis of socio demographic characteristics, place of residence and cancer stages. The study showed that there is a significant reduction in total costs when hypofractionated radiotherapy is adopted in breast cancer treatment. This was more pronounced when patients are treated in telecobalt machine. This throws light on significance of adopting hypofractionated approaches as a national policy to reduce resource utilization while maintaining the efficacy.

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Appendices

ANNEXURE – I

INFORMED CONSENT FORM FOR SUBJECTS

Study Title: ECONOMIC EVALUATION AND ASSESSMENT OF EARLY TOXICITY OF HYPOFRACTIONATED RADIOTHERAPY COMPARED TO STANDARD FRACTIONATION IN BREAST CANCER

Study Number: _____

Subject's Initials: _____ Subject's Name:_____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated……..for the above study and have had the opportunity to ask questions

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Investigator of the clinical trial, others working on the trial, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes.

(v) I agree to take part in the above study.

Signature or Thumb impression of the Subject / Legally acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

or

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

ANNEXURE – II
INFORMATION SHEET

Department of Radiotherapy CMC Hospital Vellore, Tamil Nadu	Informed Consent Sheet No.....

Title of Research :ECONOMIC EVALUATION AND ASSESSMENT OF EARLY TOXICITY OF HYPOFRACTIONATED RADIOTHERAPY COMPARED TO STANDARD FRACTIONATION IN BREAST CANCER

Person carrying out the research: Dr. Chandralekha K

Part I: - Information sheet

Introduction- I am Dr.Chandralekha, post graduate student in the department of Radiotherapy. I am doing a research onEconomic evaluation and assessment of early toxicity of short duration radiotherapy compared to standard radiotherapy in breast cancer. I am going to give you the information regarding my study and invite you to be a part of my study. At any point of time if there is any doubt or if you are not clear with the study protocol please feel free to ask.

Purpose of the research: Radiotherapy is essential for patients with early and advancedbreast cancer for reducing chances of disease recurrence. This study is done to analyse the expenditure and early toxicity of the patients undergoing two different radiotherapy schedules after mastectomy.

Participant Selection: You have been invited to participate in this study because you have been diagnosed to have carcinoma breast and you will be treated with one of the radiotherapy schedules. We will provide a questionnaire for economic analysis of your radiotherapy regimen.

Voluntary participation: Your participation in this research is entirely voluntary. It isyour choice whether to participate or not.Whether you choose to participate or not, your managementdoes not change at all. You may even change your mind and withdraw even if you had agreed earlier.

Information on the Research study:

Patients with breast cancer treated with Radiotherapy to reduce recurrence. We provide a validated questionnaire related to economic evaluation of radiotherapy schedules. The costs and expenditure of the two different radiotherapy schedules are analysed.Early toxicity occurring in both these schedules also analysed.

Side effects: This is a cross sectional study based on questionnaire posing no harm to the patients.

Risks: The study has no risks to the patients.

Confidentiality: Your name will not be mentioned anywhere in the data sheet or the final published study. Your data will bear a study number and the same number will be used till analysis**.**

Sharing of the result: The result of research is the property of Christian Medical College and **. I may publish it (Q-K , Statement modififed)** in a journal or at a conference

Right to refuse or withdraw: You do not have to participate in this research if you do not wish to. It is your choice and all your rights will be respected.

This study has been reviewed by [IRB, Christian Medical College], which is a committee whose task is to make sure that research participants are protected from harm. It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

Contact

Dr.Chandralekha
PG registrar, Radiotherapy,
CMC Vellore
Contact number: 9841001766

ANNEXURE – III

DATA SHEET

Name of the patient:

Age:

Address and Phone number:

Employment:

Marital status:

Guardian / Husband's occupation:

Children:
Number and education:

Other dependents:

Stage of tumour:

Comorbiditites:

Surgery: Date of surgery:

Radiation :
Date of starting radiotherapy:
Date of completion of radiotherapy:
Regions treated: Dose of radiotherapy:
Any side effects/complications due to treatment-
Stay in hospital for treatment of complications

THE PURPOSE OF THE QUESTIONNAIRE

1. In this questionnaire we are trying to find out about the costs to you, the patient and also the costs to your family of the radiotherapy treatment you have been receiving for carcinoma breast. Your answers are important because they will give persons who make decisions about patient treatment within the National Health Service an idea of how much the treatment costs you.

2. Please answer every question. If you are not sure or cannot remember the exact details, pleasegive the best answer you can. If you have a problem in answering any question, please write that problem beside the question.

3. The information that you provide will be completely confidential. Your answers will be combined with the answers of other patients involved in the study and reported in such a way that it will not identify you or influence your pattern of treatment.

4. If you would like any further information about this study please contact Dr Chandralekha at Dept of Radiation Therapy, Christian Medical College on 0416 2283145 or 0416 2282465.

ANNEXURE -IV

QUESTIONNAIRE

DIRECT MEDICAL COSTS:

1. How much did you pay during treatment? Please indicate what were they for, in the table below. Write the purpose and the amount of money spent.

Purpose	Amount spent
Investigation	Rs.
Treatment	Rs.
Bed Charge	Rs.
Food	Rs.
Medicines	Rs.
Miscellaneous	Rs.

2. How much do you pay for your accommodation per day?

COSTS AFTER TREATMENT UPTO 6 WEEKS:

3. During treatment how many times have you visited the hospital (regular treatment and treatment of side effects if any)? Please writethe number of times in the box below.

Number of times

4. During treatment did you visit a health care professional other than for your normal *hospital appointments* related to breast cancer and for which you made some payment? Please circle the appropriate answer (*use 'response' if preferred*).

Yes …….....1

No…….....2

5. In the table below please write the number of visits to each type of professional listed and the amount of any payments made. Please write zero if there were no visits to each of the professionals listed.

Care professional	Number of visits	If you had to pay for any of these services please indicate how much for each visit
Hospital doctor or consultant		Rs.
Nurse		Rs.
Physiotherapist		Rs.
Others (please specify)		Rs.

DIRECT NON-MEDICAL COSTS:

6. When you visited the hospital, how much did you spend to travel there from your home? Please write the total amount including the amount for return journey.

   Cost Rs: (including return journey)

7. When you visited the hospital, if anyone (friend/relative) accompanied with you? If yes and If your main companion normally travelled with you mention amount spent on journey for companion in the box below.

   Cost of journey Rs: (including return journey)

8. In case your from another state ,how much did you spend for the travel? (including return)

   Did anybody accompany you, If so mention the expenditure for them

9. How much did you spend for your companion/care taker accommodation per day?

10. How much amount did you spend on food per day for companion/care taker?

HOME HELP:

11. During treatment have you been assisted and/or cared for by a home help in your home because of your *breast cancer*? Please circle the appropriate answer.

    Yes …….....1

    No …….....2

12. During treatment how often has a home help assisted and/or cared for you in your home because of your *breast cancer*? Please write the number of visits or care episodes in the box below.

    Number of visits

13. What was the average cost of a visit? Please write the average cost of a visit in the box below.

    Average cost of a visit: Rs

14. Have you applied for insurance? if yes money spent to get insurance assistance?

PRODUCTIVITY COSTS:

15. What is your main occupation?

……

16. If you took time off from paid work (or business activity if self-employed) to come to the hospital approximately how much days didyou take off work (or business activity if self-employed)? Please write the number of days in the box below.

    Number of days:
    With pay:
    Without pay:

17. Did you lose earnings as a result? Please circle the appropriate answer and mention how much is the loss of pay?

    Yes 1
    No 2
    Loss of pay: Rs

18. Did your time off from paid work affect your increment/promotion?

19. How many days did your companion/care taker take off from work because of your current treatment?
20. Loss of wages for your companion/care taker for taking off from work – Rs.

ANNEXURE – V

ACCOUNT DEPARTMENT PROFORMA – TREATMENT PROCEDURE COSTING

CHRISTIAN MEDICAL COLLEGE – VELLORE. DEPARTMENT OF RADIOTHERAPY						
PARTICULARS FOR COSTING OF (NAME OF PROCEDURE)						
1.DETAILS OF STAFF						
NAME	EMP NO.	DESIGNATION		TIME CONTRIBUTION		WORK DESCRIPTION
					MINUTES	
2.EQUIPMENTS / INSTRUMENTS						
NAME OF EQUIPMENT	QTY	PROCEED	EB	YEAR	PURCHASE	AMC
	(Nos.)	TIME	OUTPUT	OF	VALUE	
		In Minutes	In watts	PURCHASE		
MEDICAL						
GENERAL						
1.AIR CONDITIONER						
2. TUBE LIGHT						
3.FANS						
4. REFRIDGERATOR						
5. HEATER						
2.STATISTICS (in Numbers)	LATEST TWO/THREE YEARS					
NAME OF PROCEDURE				YEAR 1	YEAR 2	YEAR 3

ANNEXURE – VI

MASTER CHART

idno	name	age	address	place	employme	maritalsta	hoccup	stage	side	machine	region	dose	ttd	
1	MANJUDAS		43 ASSAM		2 HOUSE WI	1	LABOURER	TXN1		2	1 SUPRA CLA		2	15
2	BHARATHI		36 CHITHOOR		1 TEACHER	1	CLERK	T2N1		2	2 SC/CW		2	15
3	THIRUMATHA		67 THIRUPPUF		2 HOUSEWIF	1	widow	T4N1		1	2 SUPRACLA\		2	15
4	SARASWATHI		60 CHITOOR		1 HOUSEWIF	1	LABOURER	T3N0		2	2 SPCLAV/CV		2	15
5	RAMAPATI		40 BIHAR		2 HOUSEWIF	1	FARMER	TXN0		1	1 CW/SUPRA		2	15
6	POORNIMA		32 VANIYAMB		1 HOUSEWIF	1	SHOE COM	T4N0		1	1 SC/CW		2	15
7	RESHMA		33 ARAKKONA		1 HOUSEWIF	1	HYNDAI CC	T2N1		1	2 SC/CW		2	15
8	SARASWATHI		51 WEST BEN(		2 g	1	LABOURER	T3N0		2	1 SC/CW		2	15
9	NIRMALA		37 NAMMAKK		2 HOUSEWIF	1	TRAVELS/D	TXN0		2	2 SC/CW		2	15
10	BASANTI MUF		45 WEST BEN(		2 HOUSEWIF	1	LABOURER	T4N0		2	1 SC/CW		2	15
11	MINU DAS		37 WEST BEN(		2 HOUSEWIF	1	GRILL WOF	T2N0		1	1 SC/CW/AXI		1	25
12	RANI		28 THIRUCHEI		2 HOUSEWIF	1	LABOURER	T3N1		1	2 SC/SW		2	15
13	CHITRA		63 VELLORE		1 HOUSSEWI	1	NOT WORK	T3N0		2	1 SC/CW		2	15
14	MARY		40 KOLAR,KAF		2 HOUSEWIF	1	LABOURER	TXNX		1	2 SC/CW/AXI		1	25
15	TULSHI ROY		45 ASSAM		2 HOUSEWIF	1	BUISINESS	T4N1		1	1 SC/CW		2	15
16	CHINNAPONA		40 DHARMAPI		1 LABOURER	1	LABOURER	T2N1		1	2 SC/CW		2	15
17	RADHA SHARI		43 WEST BEN(		2 HOUSEWIF	1	LABOURER	T4N0		1	1 SC/CW		1	25
18	VIJAYABHARA		52 GODAVARI		2 HOUSEWIF	1	CLERK	T4N0		2	2 SC/CW		2	15
19	SHARMILA GI		46 KOLKATA		2 HOUSEWIF	1	BANK EMP	T3N0		2	2 SC/CW		2	15
20	JOYMATI SIN(		42 ASSAM		2 HOUSEWIF	1	PRIVATE C(	T2N0		2	1 SC/CW		1	25
21	USHA SHARM		56 PATNA		2 housewife	1	shop	t4n1		2	2 SC/CW		2	15
22	SUGUNA		50 THIRUVANI		1 HOUSEWIF	1	LABOURER	T3N1		1	2 SC/CW		2	15
23	KAJAL DAS		54 MIDANPOF		2 HOUSEWIF	1	LABOURER	T2N1		1	1 SC/CW		2	15
24	KAMATCHI		46 VELLORE		1 COOLIE	1	LABOUREE	T2N3		1	2 SC/CW		1	25
25	BUDHNI DEBI		57 WEST BEN(		2 HOUSEWIF	1	SHOP	T3N1		1	1 CW/SC		2	15
26	SHEELA CHER		57 KOLLAM KI		2 HOUSEWIF	1	OFFICER/B	TXNX		1	2 SC/CW		1	25
27	ANANDHI		44 vellore		1 LABOURER	2	nil	T3N1		1	1 SC/CW		2	15
28	BULA RANI D/		47 WEST BEN(		2 HOUSEWIF	1	LABOURER	T3N1		1	1 SC/CW		2	15
29	SHEFALI		34 WEST BEN(		2 HOUSE WI	1	BUISINESS	TXNX		1	1 SC/CW		2	15
30	NIRMALA PAL		55 WEST BEN(		2 HOUSEWIF	1	SHOP	T3N2		2	2 CW/SC		1	25

se	n12trt	insurance	amount	n14food	n17accom	n24total	n25os	n26osa	n27accom	n28food	lossacc
GRADE 1	17125	2	0	8000	3500	300	3000	3000	3000	1000	8000
NIL	34220	2	0	800	0	3750	0	0	0	500	10000
grade 1	34220	2	0	4000	2000	300	250	500	2000	2000	10000
HYPERPN/I	34220	2	0	3000	2000	300	200	200	2000	2000	2000
GRADE 2	17165	2	0	2500	2500	450	200	1000	2500	2000	8000
GRADE1	0	1	17840	600	0	0	0	0	0	0	2000
GRADE1	0	1	34220	2000	0	1000	0	0	0	1000	2000
GRADE 2	17420	2	0	1000	2000	150	200	1000	2000	1000	5000
NIL	0	1	100	4000	3000	0	0	0	1000	4000	6000
NIL	17125	2	0	2000	2000	0	1000	2000	2000	2000	8000
GRADE1	17125	2	0	3000	3000	500	1000	1500	3000	3000	11000
GRADE 1	0	1	34220	2000	3000	300	0	800	1000	2000	3000
GRADE 1	0	1	17125	2000	0	750	0	0	0	1000	3000
GRADE 2- 3	34220	2	0	3000	3000	0	1000	1000	3000	2000	8000
GRADE 2	17125	2	0	3000	3000	300	1000	1000	2000	2000	6000
GRADE 1	0	1	34220	2500	450	300	400	500	450	1000	6000
GRADE 1	18995	2	0	4000	4000	500	1000	2000	3000	3000	9000
GRADE 1	34220	2	0	4000	2000	300	300	600	2000	3000	6000
grade 2	34220	2	0	4000	1500	0	2000	2000	1500	2000	7000
grade 1	18995	2	0	4000	4000	0	6000	6000	3000	3500	12000
GRADE 1	18670	2	0	3000	2500	450	1000	1000	2500	2000	8000
GRADE 1	0	1	34220	2000	1000	0	0	0	1000	1000	3000
GRADE 2	10122	2	0	3000	2500	450	1000	2000	2000	2000	9000
GRADE 1	0	1	34220	2000	0	1250	0	0	0	1000	6000
GRADE 1	17125	2	0	3000	2500	0	500	1000	2500	2000	5000
GRADE1	34220	2	0	7000	7000	1875	2500	2000	4000	4000	15000
GRADE 1	4280	2	0	1000	0	450	0	0	0	1000	1000
GRADE 2	18890	2	0	2500	3000	300	800	2000	2000	2000	7000
GRADE 1	17125	2	0	2500	2000	300	600	1200	1000	2000	7000
GRADE 1	31100	2	0	5000	4000	750	2000	2000	3000	3000	15000